NIH AIDS Research Program Evaluation

ETIOLOGY AND PATHOGENESIS AREA REVIEW PANEL

Findings and Recommendations

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Executive Summary

A. Prologue to the Panel's Conclusions and Recommendations

In reviewing the NIH effort in the area of etiology and pathogenesis, the Panel was impressed with the remarkable achievements to date in identifying and characterizing the virus that causes AIDS, the depth and comprehensiveness of the research portfolio, and the plans to address the complex outstanding scientific issues in the future. The Panel's recommendations are therefore not a call for a paradigm shift but rather constructive advice on what to emphasize and what to do to attract more scientific talent to the field and improve the quality, effectiveness, and AIDS focus of the research.

To sustain, renew, and support exceptionally creative and productive scientists and science, the Panel makes a number of cross-cutting recommendations for:

1. Increased emphasis on investigator-initiated research through doubling of the R01 pool of funding.
2. Continued, but more selective, use of RFAs with set-aside funding in critical areas of research not addressed by the R01 mechanism; these critical areas should be identified in an ongoing conjoint effort of the ICDs, OAR, scientific advisors, and community representatives.
3. Increased support to encourage long-range discovery research and the entry of both new and distinguished established scientists into the field.
4. Increased focus on understanding the basic immunology of infected and uninfected human beings and primates and on efforts to attract immunologists to the field.

Implementing these recommendations will require fiscal and other resources, primarily primate animal models and tissue specimens. The Panel identified as potential fiscal reservoirs:

5. Redirection of funding away from research projects, both extramural and intramural, that are judged to be of lesser quality or relevance.
6. Redirection of funding for research or infrastructure currently designated as AIDS-related but which does not meet the rigorous criteria called for by the Panel.

The Panel urges greater access to primate animal models and tissue specimens through:

7. Open competition and expert peer review to increase access to funding at Regional Primate Research Centers (RPRCs) and the neuro-AIDS centers for training and research.
8. Restoration of resources to the most relevant nonhuman primate model.
9. Greater involvement of the extramural scientific community in the design of natural history studies to engender hypothesis-driven collection of specimens.
10. Separation of collection of specimens from access to specimens by all qualified investigators.

The Panel concludes that organizational changes can be made that will improve the quality and AIDS focus of pathogenesis research and makes cross-cutting recommendations that include:

11. Open competition and comparable criteria for funding for all mechanisms and programs.
12. Improved peer review, from the composition of the study sections to shared oversight by the ICDs and OAR.
13. Improved management and AIDS focus achieved by:

- Fully vesting OAR with the fiscal and scientific authority to coordinate the total NIH AIDS effort, intramural and extramural, but operating by regularly and systematically soliciting advice from leading scientists and community representatives in the formulation and evaluation of its plans for pathogenesis research;
- Restructuring the AIDS information retrieval system; and
- Devising a mechanism to define AIDS-related research (ARR) that is both rigorous and evolving in response to new scientific priorities.

In the aggregate, these changes should make it possible to redirect resources and attract outstanding scientists to addressing issues of highest priority in the area of etiology and pathogenesis.

B. Introduction and Charge to the Panel

In the quest for vaccines to prevent HIV infection and better drugs to contain infection and treat the opportunistic infections (OIs), tumors, and other manifestations of a dysfunctional immune system, we need a better understanding of how HIV infection is established and what causes the profound immune deficiency and terrible complications accompanying infection. What role do each of the viral gene products play in the viral life cycle in cells and in the infection *in vivo*? How is HIV transmitted, particularly across the mucosal barrier? What contribution does the immune system make to controlling infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other organ systems HIV afflicts?

What is the relationship of HIV infection to the associated malignancies and OIs? What host factors and cofactors influence the course and outcome of infection?

These questions define the central contemporary issues in the area of etiology and pathogenesis of HIV infection. The Etiology and Pathogenesis Area Review Panel was constituted to assess the overall NIH effort in addressing these issues, now and in the future. The Panel was charged with: (1) identifying and prioritizing the scientific issues, opportunities, and advances needed at this stage of the epidemic; (2) from that prospective perspective, assessing the scope, quality, focus, and coordination of research currently supported by the NIH; and (3) making recommendations on what the NIH should do in the future to reconfigure and redirect its programs and resources to have the greatest impact on the AIDS epidemic.

C. Scientific Issues and Priorities

The Panel identified the outstanding scientific issues and opportunities in the area of etiology and pathogenesis and prioritized these issues based on their potential importance for the development of vaccines and drugs to prevent and control infection, or insights into how a normal functioning immune system might be maintained despite infection. In general agreement with ICD research agendas and the conclusions from recent reviews and analyses by the ICDs, coordinating committees, and OAR working groups, the Panel has identified the most important scientific issues as being:

1. The highest priority is understanding the pathogenesis of immune dysfunction and depletion and the failure of the immune system to reconstitute itself in HIV infection. This can be achieved by understanding the following issues:

- The basic cellular and developmental biology of all CD4 progenitors;
- The transmission of infection, pathogenetic events in acute infection;
- Host immunity and correlates of immune protection, especially identification of the critical cellular and humoral immune elements that prevent infection or eliminate or suppress HIV, HIV-infected cells, or opportunistic pathogens;
- The role of viral variation in these processes;
- A detailed definition of virus-host cell interactions at all stages of the HIV life cycle;
- The structure and function of all the viral gene products and the regulation of viral gene expression; and
- How to improve biologically relevant *in vivo* models.

2. Although the pathogenesis of HIV-related OIs, malignancies, neurological disease, and other organ system involvement rank somewhat lower in order of priority, these are nonetheless issues of exceptional importance that must continue to receive attention and resources. This requires study of:

- The pathogenesis of HIV-related opportunistic infections and malignancies;
- The pathogenesis of HIV-related neurological disease; and
- Wasting, decreased growth, and other organ system (cardiovascular, renal, gastrointestinal) involvement in HIV infection.

In accord with the forward-looking assessment of research in the area of etiology and pathogenesis, the Panel also anticipates that new drugs and new drug combinations will have beneficial effects on the course of HIV infection and alter its manifestations. It is thus likely that new issues in HIV pathogenesis will arise in the future that will need to be addressed. Even more important are the dividends that could be reaped in the future from research on the etiology and pathogenesis of HIV infection. From a deepened understanding of the human immune system, HIV, other viruses, and microorganisms, we anticipate discovery of new approaches to intervening in the decline of immune function with age and disease and new therapies for infections.

D. Conclusions and Recommendations

The Etiology and Pathogenesis Panel assessed the NIH effort in its area, identified opportunities to strengthen that effort, and sets forth below its conclusions and recommendations on how these goals might be accomplished. While some of the recommendations focus on structure and organization, the Panel's main concern has been with suggesting changes in process that are sufficiently generic and flexible to accomplish the primary objectives of sustaining, recruiting, and training outstanding scientists to respond to current and future scientific challenges.

Status of the NIH AIDS Research Effort: High Praise Overall but Room for Improvement

The Panel first goes on record in its praise for what the NIH has already achieved in responding to an epidemic of a fatal infection in just over a decade. The rapid identification and characterization of the virus that causes AIDS, and development of strategic plans and a research portfolio to address the complex outstanding scientific issues of HIV infection are truly impressive achievements. Partially offsetting this positive assessment, however, is considerable evidence, documented in the full Panel report, of work of disappointing quality and relevance. The Panel particularly singled out the National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), and National Institute on Alcohol Abuse and Alcoholism (NIAAA) for their substantial support of research of little or tangential relevance to finding answers to the central questions of HIV pathogenesis. Redirecting resources from these programs is an essential and urgent priority to renew the program and to bring new scientific talent into the field to address the outstanding and unresolved scientific issues.

Recommendations

1. Improve the scientific portfolio: programs and human and fiscal resources.

The Panel discussed at length mechanisms to develop and maintain an optimal and balanced scientific portfolio, launch new programs, and allocate resources. The Panel believes that the mechanisms and process that shape the scientific portfolio could also be used to serve other important objectives: attracting new highly qualified junior investigators and leading senior investigators in other fields to AIDS research, and providing more training opportunities for the most promising students and postdoctoral fellows.

There was a resounding consensus that the resources currently available to support investigator-initiated research (R01s) are simply insufficient and that this mechanism generally has been, and will continue to be, the best mechanism to address the scientific issues. For a number of reasons, many historical, the R01 pool for AIDS research is less than half of the support by all mechanisms. The current funding levels of grants that are reviewed by AIDS study sections are extremely low. Many AIDS grant proposals that certainly would deserve support if sufficient resources were available go unfunded. Of the proposals that ultimately do get funded, multiple cycles of grant submission are often required. The resulting delays in initiating potentially important AIDS research programs inevitably slows the rate of progress that can be made against the disease. Indeed, the original (and important) intent of the process of accelerated

review for AIDS research proposals has become virtually irrelevant when so few proposals are funded in each grant cycle. Another negative consequence of the intense competition for research dollars is that many investigators feel that they must respond to the real or perceived pressures exerted by study sections to present conservative proposals that have a very high likelihood of success. As a result, creativity and innovation are often penalized rather than rewarded and research progress may be slowed. Further, the tight competition for grants has led study sections to heavily favor applications containing extensive preliminary data. While this is an important criterion by which to evaluate the merit of grant application, it represents a major barrier to attracting new investigators to the field of AIDS research.

1a. Double the support for unsolicited investigator-initiated AIDS research (even if this results in different paylines for AIDS and non-AIDS research).

The Panel also sees a need for selective use of other mechanisms of funding, and for long-term stable support to maintain focus and balance in the portfolio, move in new directions, and encourage innovative research with long-range objectives.

1b. Use RFAs with set-aside funding selectively, both to focus attention on important areas of pathogenesis research and to bring established or new high-caliber scientists into the field.

This recommendation arose out of discussions of critical shortcomings in our understanding of human immunology and mucosal immunity and of two superficially disparate examples of how successful programs in AIDS pathogenesis research had been initiated in the past. The first is a National Institute of General Medical Sciences (NIGMS) program on the structural biology of HIV that brought together distinguished investigators to work on HIV through well-organized interactive program project grants. The second, a program of the National Institute of Allergy and Infectious Diseases (NIAID), is an RFA with set-aside funding that reflects in large measure NIAID's response to previous reviews of the pathogenesis agenda in 1993 calling for substantially increased efforts to understand sexual mucosal transmission of infection. These programs have the following in common:

- Well-informed NIH staff working with the extramural scientific community through personal contacts, program reviews, workshops, and conferences to identify important areas of research;
- Involvement of the non-Governmental scientific community in formulating and disseminating the announcement of the initiative in a way that encourages scientists from other fields to apply and consortial (“dream team”) approaches by collaborating investigators from different institutions/sectors;
- Set-aside funding.

2. Enhance the emphasis on long-range discovery research in areas of highest priority, especially human immunology.

Another recurring theme in the Panel's discussions was the need to engage exceptionally distinguished scientists in AIDS pathogenesis research and encourage long-term research directed at fundamental and central issues. These objectives cannot be accomplished without long-term support and other incentives to encourage distinguished scientists to undertake innovative high-risk but high-payoff discovery research, e.g., sponsored by Howard Hughes Medical Institute (HHMI). Greater use of Merit awards, supplemental funding for senior investigators, and consortial R01s are some ways the NIH might encourage innovative research.

2a. Use Merit and similar awards (e.g., The Javits Award) and create incentives to encourage long-range and innovative research.

It was also clear to the Panel that a better understanding of basic immunology in infected and uninfected human beings and primates is essential to understand the pathogenesis of infection and disease and to provide the foundations for development of long-lasting, safe, and effective treatments and vaccines. The Panel suggests that OAR and the NIH should actively encourage increased efforts toward understanding fundamental, primate, human, and HIV-specific immunology and strive to draw high-caliber immunologists not now involved in AIDS research into studying HIV/SIV immunology.

2b. Convene a series of meetings of expert non-AIDS and HIV/SIV immunologists to consider ways of engaging immunologists in the effort to address the critical issues and to overcome the challenges of studying the immune systems of genetically complex humans and nonhuman primates.

2c. Provide supplemental funding to attract immunologists into the field.

2d. Establish consortial approaches between basic immunologists and investigators currently engaged in AIDS research. The anticipated benefits of the consortial mechanisms include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; facilitating exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows will go into AIDS research.

Where will the resources come from to follow these recommendations?

From its review of the etiology and pathogenesis portfolio and examination of intramural research, contracts, and cooperative agreements, the Panel, with near unanimity, concluded that one-third to essentially the entire pathogenesis portfolio of some ICDs, such as NIAAA, was either (1) not relevant or of lesser relevance to central AIDS research priorities, (2) of dubious quality, or (3) of indeterminate nature or quality (e.g., generically described awards to fund centers, contracts, cooperative agreements, and intramural programs).

2e. Funds from these programs of poor quality, productivity, and relevance should be redirected.

2f. Rigorous guidelines on what constitutes AIDS and ARR will likely free up needed resources.

For example, generic investigations of opiate receptors, oncogenes, and viral oncogenes currently designated ARR by the ICDs will not, in the Panel's view, meet these rigorous criteria, and their substantial funding can and should be redirected at the time of recompetition and renewal. Some of the AIDS monies currently allocated for etiology and pathogenesis are now expended within the AIDS Clinical Trials Groups (ACTGs), statistical centers, and the National Center for Research Resources (NCRR) for general biomedical infrastructure support. These funds might have greater impact if actually used to support basic research on HIV pathogenesis.

2g. OAR should establish mechanisms involving the extramural scientific community, such as the annual scientific planning workshops, for open discussion and decision on the portion of the AIDS research budget that would be appropriate to use to support the general costs of biomedical research (matched by services received) and of AIDS research that are nominally designated currently as etiology and pathogenesis.

3. Improve peer review, quality control, and AIDS focus.

The Panel's conclusions that a substantial portion of the portfolio is of disappointing quality and relevance and that there are examples of a “closed-shop” mentality in the use of some of the resources immediately implies the need for improved peer review, AIDS focus, and open competition.

3a. Open competition for funding from all sources: grants, contracts, cooperative agreements, and centers should take place.

3b. OAR should apply comparable NIH-wide criteria in evaluations of intramural and extramural research by the quality of science and the qualifications and productivity of the scientists and by the focus and potential impact on AIDS.

3c. These evaluations should be recurring regular reviews of all programs (extramural and intramural) with NIH funding by reviewing bodies with a majority of non-Government scientists.

3d. Peer review should be improved.

The paramount consideration in constituting study sections and other reviewing bodies is scientific expertise, as determined by a previous record of scientific accomplishments, productivity, and knowledge of the field relevant to the review. Possible mechanisms to ensure high-quality reviews responsive to the changing scientific issues include working with learned societies to identify distinguished scientists with a broad range of expertise to serve on study

sections, using voting ad hoc members freely, and exercising flexibility on diversity and term limits for study sections.

The review of senior investigators should be largely by merit or recent track record; review of junior or new investigators to AIDS research should be based on the research proposal.

3e. The research focus on AIDS should be improved.

The separation of programs from review has inadvertently created barriers between the Division of Research Grants (DRG) and the ICDs that have created difficulties in shaping an AIDS portfolio that is responsive to the scientific issues.

- The DRG and study sections need to be better informed of OAR scientific priorities and need to view the relevance of a proposal to these priorities as an important criterion for funding. (Earlier recommendations in this document suggested mechanisms to enhance communication between study sections and programs.)
- The Panel endorses changes in DRG recommended in the Cassman Report, which call for a peer-review oversight group (PROG) and peer review conducted by both DRG and ICDs, as appropriate. A body similar to PROG should be established for intramural research.
- OAR should have separate and parallel input to the final evaluation and ranking of review panels. For grants that remain classified as AIDS/AIDS-related following council review, funding decisions should be made by the Institute Director in consultation with the Director of OAR.

4. Formulate and implement mechanisms to increase access to and improve the use of critical resources such as RPRCs and central repositories.

Animal models are a precious resource, not just to answer the questions of an individual investigator but as a shared resource for the scientific community. This is particularly the case for nonhuman primates, which are critical for studies of immunity and pathogenesis, for evaluating genetically engineered changes in the viral genome, and for development and testing of drugs and vaccines. While the ungulate models, FIV, HuSCID, and transgenic models will continue to be useful for certain issues of pathogenesis, the primate model and the primate centers are of preeminent importance. Access to this model and the RPRCs must be facilitated and the review of the Centers and investigators improved by the following recommendations:

4a. Competition for AIDS research project funding by NCRR at RPRCs should be opened to all extramural investigators, rather than only to permanent Center staff.

4b. The NCRR study sections that review the RPRCs should incorporate expertise in AIDS and ARR.

4c. There should also be open competition for all relevant animal cost-funding of DRG-reviewed grants through a regularly recurring RFA.

4d. In view of the limited utility of chimpanzees for studies of AIDS pathogenesis, resources currently set aside for breeding and maintaining chimpanzees would be better used by NCRR for openly competed studies in macaques.

The Panel strongly supports NCRR's plans to expeditiously conduct a review of the chimpanzee research program under the auspices of the National Academy of Sciences.

Similarly, repositories of molecular and immunological reagents and banks of tissue samples generated in various cohort studies are critical and limited resources for all aspects of studies of pathogenesis directed to understanding interactions between HIV and its human host. A centralized system to collect, catalog, and distribute reagents is largely a success story, but there is a great need for better access to clinical samples whose collection should be guided and driven by the research questions.

4e. OAR, in conjunction with the ICDs and extramural scientific community, should establish NIH-wide guidelines for access to clinical samples.

- The type and frequency of samples collected should be appropriate to the investigation. This is a moving target that will require an explicit mechanism to ensure interaction between investigators, clinicians, and those responsible for the repository to decide what should be collected and priorities for distribution.

- Qualified investigators must have better access to samples. Guidelines currently being developed, e.g., at NIAID, should convey a sense of public ownership and should separate collection of samples from access to them by all qualified investigators. The sample repository should be seen as an opportunity to link basic and clinical investigators in collaborative studies.

5. Define and focus the scientific portfolio of AIDS and AIDS-related research and associated program resources.

To align scientific priorities with programs and resources, the NIH needs to develop better information systems and be able to properly identify resources that are appropriately designated AIDS or ARR.

5a. The NIH and OAR should develop a new AIDS information system that lists grant titles and numbers, investigators' names and institutions, dollar amounts, funding ICDs, and abstracts; is searchable by these parameters and by topic area (e.g., MESH headings); lists publications stemming from the research; can be applied equally to all NIH-funded AIDS research, both intramural and extramural; and is user-friendly and accessible to all those involved in the evaluation of NIH-funded AIDS research.

This recommendation arose out of the Panel's frustrations and inordinate labors with the current arcane system, which is so limited that it slowed and compromised assessment of the portfolio and raised serious issues of accountability. Intramural and some extramural awards (such as large program project grants, core facilities, primate research centers, clinical research units,

and cooperative agreements) were either scarcely described, or described so generically that it was difficult, if not impossible, to assess programs that in the aggregate consume tens of millions of dollars.

5b. Establish an evolving mechanism to define ARR through a conjoint effort of the ICDs and OAR, with involvement of the extramural research community. This definition should be broad but rigorous, consistent across ICDs, and updated annually. An explicit defensible rationale to define ARR should be linked to scientific issues and strategies and should be redefined as scientific progress reveals new areas of relevance. Research proposals should be predesignated by the principal investigator (PI) as AIDS or ARR and reviewed by appropriate panels that include OAR staff.

Resources devoted to ARR should be clearly identified on a reasonable rather than arbitrary basis. For example, 5 percent of NIAID's AIDS Clinical Trials Unit (ACTU) budget is currently designated as pathogenesis-related whether or not these funds are actually used to support research in this area.

6. Maintain a strong OAR.

It is clear to the Panel that OAR is both essential and particularly well positioned to facilitate future progress. NIH AIDS research must be a united effort that extends beyond the boundaries and distinctive missions of the individual ICDs or divisions between intramural and extramural research. OAR has the overarching mandate for coordination that links investigators and programs and averts the risks of duplication, overlaps, and loss of focus inherent in any complex undertaking.

To successfully carry out its role of coordinating NIH-supported AIDS research across the NIH, the Panel believes OAR must have the scientific authority and fiduciary responsibility for intramural and extramural AIDS research. In addition, OAR should have other responsibilities, as follows:

6a. OAR should set the scientific agenda and priorities in a collaborative effort with the directors of the ICDs, coordinating committees, working groups, councils and advisory bodies, non-Government researchers, and community representatives. To better communicate scientific priorities and funding, relevant study section chairs should be included in the process of setting the scientific agenda.

6b. OAR should align programs and resources by having and exercising fiduciary control over all NIH AIDS programs (not only the control over new and competing funds that were assigned to OAR in the NIH Revitalization Act of 1993), including intramural research, contracts, and cooperative agreements. Without central fiscal authority to fund scientific priorities, the identification of these priorities becomes a meaningless exercise.

6c. OAR and the ICDs should continue to regularly and systematically solicit advice from leading Government and non-Government scientists in the formulation and plans for pathogenesis research.

Introduction

Charge to the Panel

The Panel was charged with identifying and prioritizing the important scientific issues and opportunities in AIDS etiology and pathogenesis at this stage of the epidemic; assessing the current status of research in etiology and pathogenesis supported by the NIH; and recommending how the NIH should redirect its programs and its resources in the future to have the greatest impact on the AIDS epidemic.

Selection and Organization of the Panel

The complex interactions between viruses and their hosts can be dissected into discrete stages and events, which for HIV generally begin with sexual transmission and end with immune depletion, opportunistic infections (OIs), tumors (OTs), and dysfunction of the nervous and other organ systems. These stages provide a structure and rationale for organizing the Panel along thematic lines to assess the NIH's effort to understand:

- Transmission of infection
- The role of innate and specific host immunity in infection and disease
- Mechanisms of immune dysfunction, depletion, and replacement
- The complications of infection: OIs, OTs, neuro-AIDS, other organ system dysfunction
- HIV structure, replication, and virus–host interactions in pathogenesis
- Animal models and pathogenesis

Most members of the Panel were selected for their expertise and contributions to these thematic areas of HIV and lentiviral pathogenesis or their record of active involvement in the area of etiology and pathogenesis. Other Panel members were chosen as distinguished representatives from the disciplines of virology and immunology who could bring a generalist perspective to the Panel's analyses and recommendations.

Process and Methodology

Viewing pathogenesis from within a framework of stages and events provided not only an organizational principle but also a methodological approach to the Panel's assessment that is at once forward-looking and retrospective. As Table 1 illustrates, under each major stage/event of infection, there remain critical questions that are unanswered or only partially answered. These questions define the scientific issues that need to be addressed in the future and the kinds of research, infrastructure, and technologies relevant to the undertaking. Within this framework the Panel conducted a retrospective review of the NIH's portfolio (see Table 2 for an illustration) for its responsiveness, focus, quality, and potential impact for each issue. In this way, the Panel identified the scientific gaps and opportunities and reached its conclusions on what to recommend to facilitate future progress.

In its assessment of the etiology and pathogenesis portfolio, the Panel utilized the NIH AIDS Research Information System (ARIS) as translated into the Panel's thematic categories by one

of the Panel's members; narrative summaries of intramural and extramural programs, by Institute; reviews and reports on pathogenesis research by Institutes and by AIDS activist groups; documents prepared by Institutes in response to requests by the Panel; OAR summaries of ICD submissions in the area of etiology and pathogenesis; and listings of grants, RFAs, and training grants by the ICDs (see the Appendix). The Panel also met with representatives of the ICDs to discuss the status of the efforts in AIDS research in the area of etiology and pathogenesis and plans for the future, sent representatives to conjoint meetings on animal models, met with representatives of DRG to discuss peer review, and assigned members to participate in separate subpanels formed, because of the overlapping scientific issues and breadth of the undertaking, to review OIs, OTs, and neuro-AIDS. The Panel as a whole met on five occasions over a period of 8 months to discuss the NIH's efforts in etiology and pathogenesis. The collectively accepted set of conclusions and recommendations are contained in the Executive Summary; the supporting data and analysis follow in this full report.

Table Legends

Table 1. An abridged illustration of the Panel's approach to assessing the NIH portfolio in the area of etiology and pathogenesis. Each stage of infection raises critical questions and issues to which the listed research, technology, or infrastructure is responsive. The NIH scientific portfolio can then be reviewed for its responsiveness, AIDS focus, and quality.

Table 2. An exploded view of that review of the general scientific issue of sexual transmission. The table lists the grants, by title, principal investigator, and level of support, that the Panel classifies as responsive to the issue of transmission and the role of virus genetic variation in transmission. From the Panel's knowledge of the field and investigator(s) and, in some cases detailed assessment of the productivity of the project, subcommittees of the Panel judged the quality and relevance of the project to addressing the scientific issue. Intramural programs were assessed from the same perspective. The Panel's recommendations flow from these reviews.

Table 1: Portion of Overview of Assessment of Portfolio on HIV Pathogenesis *In Vivo*

Time	Major stage/event in HIV infection	Critical questions	General scientific issues	Relevant research/ technologies/infrastructure	Recommendations
0	HIV in infected sexual fluids crosses the mucosal barrier In so doing, surmounts physical and chemical barriers	Relative importance of cell-free (CF) vs. cell-associated Virus types involved in transmission (genotype, phenotype, tropisms) Differences in virus in blood and genital secretions Role of STDs and other cofactors in transmission Natural defense mechanisms	Sexual Transmission Virus genetic variation and transmission	Temporal sequence of events in non-human primate models Analyses of transmission in high-risk cohorts Characterization of viruses in blood and genital secretions Cohort studies/discordant couples Specimen repositories	Optimize use of primate centers, cohort studies, specimen repository Use RFAs and long-term support selectively
hours/ days	Virus infects cells at portal of entry Infected cells encounter innate defenses; NK cells, interferons (IFNs); and specific host defenses: cytotoxic T lymphocytes (CTLs) Infected cells reach draining regional lymph node	Cells involved in establishing infection at portal of entry (macrophages, mo; Langerhans cells, LH) Nature of infection: restricted or productive Role of innate defenses in transmission Role of CTLs in control of infection Role of suppression of viral replication by CD8+ T lymphocytes	Viral-host cell interactions Host Defenses and acute infection	Virus structure, replication accessory genes Methods to characterize viral load, viral-host interactions, *in vivo* systematic, quantitative characterization of the numbers and types of cells in HIV infections; timing and relationship to transmission and outcome Analysis of virus-specific CTLs, antibodies, immune correlates in long-term nonprogressors and survivors, breakthrough infections in vaccine recipients	Double investigator-initiated AIDS research Define and focus AIDS research; improve review
weeks/ months	Viral replication Viremia Dissemination throughout lymphoreticular and other organ systems Virus-specific antibodies appear Viral titers generally decline	Control of infection by specific host defenses Alternative explanations: Availability of permissive activated CD4+ T cells Autochthonous replication Possibility of deleterious effects of host defenses, e.g., immune enhancement			

Note: See Table 2 for review of portfolio for responsiveness, focus, quality, and potential impact.

Table 2: **Pathogenesis *In Vivo*** (Exploded version)

General Issues	Relevant Research/Technologies/Infrastructure	Review of Portfolio for Responsiveness, Focus, Quality Impact	Level of Support (in $1,000s)
Transmission	Characterization of viruses in blood and genital secretions, types and quantities by appropriate methods	<u>Transmission</u> Immunobiology of HIV-1 infection in mucosa (Smith P)	$202
		Women and infants transmission study (WITS II) (Tuomala R/McIntosh K)	196
Sexual	Maintain cohort studies and specimen repositories	Women and infants transmission study (WITS II) (Tuomala R/Roberts D)	275
Parenteral	Frequent sampling of high-risk cohorts	HIV transmission and barrier contraception (Spieler J)	1,150
Perinatal	Studies of discordant couples	Feline FIV as model for perinatal transmission of HIV (Sellon R)	78
	Impact of treatment on transmission	Provide regional primate center support (Wiley J)	110
Genetic variation	Large-scale studies of impact of treatment of STDs on transmission	HIV placental infection—*in vitro* experimental models (Nahmias A)	282
	In vivo analyses of NK cells	SIV pathogenesis during ontogeny (Ruprecht R)	304
	IFNs	SIV infection of syncytiotrophoblasts *in vitro* (Golos T)	159
		Interaction of HIV with isolated placental cells (Douglas G)	196
		Viral and immune correlate of perinatal HIV transmission (Brokowsky W)	532
		Syncytiotrophoblast IGG Fc receptors and HIV infection (Sedmak D)	228
		HIV-1 transmission *in vivo* (Pomerantz R)	241
		Mechanisms of transmission of HIV (Phillips D)	250
		Heterosexual transmission and the natural history of HIV (Allen S)	604
		Women and infants transmission study—Chicago (Rich K/Garcia P)	101
		Women and infants transmission study—Chicago (Rich K)	1,264
		Women and infants transmission study (WITS II) (Shearer W)	1,121
		Women and infants transmission study (WITS II) (Tuomala R)	935
		Women and infants transmission study II—Puerto Rico (Diaz C)	1,200
		Semen cofactors in the transmission of HIV-1 (Anderson)	207
		SIV model of mucosal immunity effects on transmission (Marthas)	275
		Vaginal immunization and challenge with cell-associated virus using SIV-rhesus macaque model of HIV infection (Marthas)	126
		Rectal transmission of SIV and latency following infection. Animal-to-animal transmission of virus (Corey)	96
		Salmonella adjuvant for mucosal immunity of SIV (Pauza)	260
		Collection of cervical vaginal lavage to assess presence of HIV and HPV in vaginal secretions (WITS)	428

I. Scientific Issues and Priorities

The Panel systematically examined the NIH portfolio in etiology and pathogenesis within the framework of the life cycle of HIV, within cells, and in infected individuals, and through this process reached its conclusions about the important scientific issues that still need to be addressed. The Panel prioritized these issues based on their potential importance for the development of vaccines and drugs to prevent and control infection or insights into how a healthier immune system might be maintained despite infection. In general agreement with ICD research agendas and the conclusions from recent reviews and analyses by the ICDs, coordinating committees, and OAR working groups, the Panel views the following as the most important scientific issues:

1. The Panel believes that the highest priority is understanding the pathogenesis of immune dysfunction and depletion and the failure of the immune system to reconstitute itself in HIV infection. This can be achieved by understanding the following:

    - The basic cellular and developmental biology of all CD4 progenitors;
    - The transmission of infection, pathogenetic events in acute infection;
    - Host immunity and the control of infection, especially identification of the critical cellular and humoral immune elements that prevent infection or eliminate HIV, HIV-infected cells, or opportunistic pathogens;
    - The role of viral variation in these processes;
    - A detailed definition of virus-host cell interactions at all stages of the HIV life cycle;
    - The structure and function of all the viral gene products and the regulation of viral gene expression; and
    - How to improve biologically relevant *in vivo* models.

2. Although the pathogenesis of HIV-related OIs, malignancies, neurological disease, and other organ system involvement rank somewhat lower in order of priority, these are nonetheless issues of exceptional importance that must continue to receive attention and resources. This requires study of:

    - The pathogenesis of HIV-related OIs and malignancies;
    - The pathogenesis of HIV-related neurological disease; and
    - Wasting, decreased growth, and other organ system (cardiovascular renal, GI) involvement in HIV infection.

In accord with the forward-looking assessment of research in the area of etiology and pathogenesis, the Panel also anticipates that new drugs and new drug combinations will have beneficial aspects on the course of HIV infection and alter its manifestations. It is thus likely that new issues in HIV pathogenesis will arise in the future that will need to be addressed. Even more important are the dividends that could be reaped in the future from research on the etiology and pathogenesis of HIV infection. From an increased understanding of the human immune system, HIV, other viruses, and microorganisms, we anticipate discovery of new approaches to intervening in the decline of immune function with age and disease and new treatments for infections.

II. Scientific Opportunities in Priority Areas Highlighted by the Review

The Panel sees scientific opportunities in each high-priority area, and presents its analysis in the same sequence as the events in the viral life cycle in cells and during infection *in vivo*.

A. HIV Genome, Structure, and Replication

There has been substantial progress in the past decade in understanding the structure and function of HIV proteins in each step in replication, but gaps remain in our knowledge, in both depth and sophistication, of the mechanisms of viral replication, from entry to release of mature progeny. Particularly fertile areas with implications in rational drug design currently include entry events (fusion, uncoating); reverse transcription, nuclear import, and integration in differentiated cells; transcriptional control and its role in HIV latent infections; and the structure and function of the viral accessory proteins involved in transactivation, cytoplasmic export of viral RNA, and enhancement of virion infectivity. There is a need for a better understanding of how viral proteins interact with cellular pathways of signal transduction that could cause immune dysfunction and depletion by, for example, inducing apoptosis. These analyses must be undertaken in biologically and clinically relevant systems and will depend for their success on the development of functional assays for each of the virion proteins. The Panel envisions increasing emphasis on primary cultures of T lymphocytes and macrophages infected with clinical isolates and greater use of the best animal model, infection of rhesus macaque monkeys with the Simian Immunodeficiency Virus (SIV), where the effects of mutations in viral structural and regulatory genes on pathogenesis can be tested.

B. Transmission, Viral Variation, and the Acute Phase of HIV Infection

The initial phase of HIV infection involves transmission of free viruses, which are invariably far less complex genetically than the swarm present in the transmitting individual or of viruses associated with cells. This occurs most commonly by sexual contact but also by parenteral and perinatal routes. Replication ensues, perhaps at the portal of entry or in the draining lymph node, and in the subsequent weeks to months HIV-1 is disseminated. This viremic phase is often accompanied by a symptomatic illness and abrupt decline in CD4+ T cells, followed by rebound coincident with the immune response and considerable clearing of virus from the bloodstream.

During this acute stage of infection, HIV-1 must breach physical and chemical barriers and elude innate host defenses early on, and soon thereafter, HIV must also evade clearance by specific cellular and humoral antiviral immune responses. Answering the outstanding questions below would clearly provide a sounder approach to preventing transmission by vaccination, virucides, or other methods:

1. Is infection transmitted by cell-free or cell-associated virus or both?
2. What cell type(s) is first infected at the portal of entry?
3. What is the genotype and phenotype of the viruses at the portal of entry? Is transmission related to cellular tropisms or variation in virion components that interact with host defenses?

4. How important a role do sexually transmitted diseases (STDs) play in transmission? What is the role of other cofactors such as hormones and the menstrual cycle?
5. To what extent do or can host factors, such as adhesion molecules, and host defenses, such as interferons, natural killer (NK) cells, complement and mucosal immunity modify or prevent transmission?
6. What role do latent and productive infections play in transmission? In acute infection and subsequent probability of progression to disease?

Prior and current investigations of transmission in cohorts, collection of blood and sexual fluids for characterization of virus, genetically and biologically, are examples of the responsive efforts supported by the NIH. There remain, nonetheless, many areas of opportunity, particularly sexual mucosal transmission, which is just beginning (through NIAID's efforts) to receive the attention it deserves as the major route of transmission. There is, however, insufficient integration of clinical and basic researchers working in transmission and inadequate mechanisms to collect and distribute appropriate specimens. More focused investigations of high-risk cohorts and discordant couples, and large-scale studies of the impact of treating STDs on HIV-1 transmission are critical. These enhanced efforts will require an increased involvement of expert virologists and immunologists in the design and conduct of natural history studies. Expanded efforts in the SIV macaque model are essential, as this represents the only system in which the temporal sequence of events can be evaluated.

C. Innate and Specific Host Defenses

Within hours to the first few days of infection, virus or HIV-infected cells must escape elimination by innate host defenses, such as NK cells, and, later, by cytotoxic T lymphocytes (CTLs) and antibodies. While HIV-1 can clearly cause persistent infections in the face of these host defenses, it is also probably true that host defenses play an important role in containing infection until the late stages of infection. Understanding why host defenses possibly succeed in preventing infection or disease at times, how the immune system may control infection for years, and why it fails to eliminate or control infection are obviously critical issues that have not been resolved despite extensive efforts. To develop effective vaccines and immune-based therapies, every aspect of host defenses thus remains a priority, with a greatly increased emphasis on human immunology and mucosal immunology. Specific areas deserving continued attention include:

1. Studies of interactions of HIV-1 and HIV-1-infected cells with innate defenses: biochemical and physiological analysis of NK cells, macrophages, complement; natural inhibitors in tissue fluids; interferons.
2. Studies of the cellular immune response: fine structure analysis of virus specific CTLs; suppression of viral replication by cytokines and other factors elaborated by CD8+ T lymphocytes; TH1 and TH2 responses in HIV-1 infection; viral antigenic variants and escape from CTLs; holes in the defense repertoire late in disease.
3. Investigations of the humoral immune response: fine structure analysis of virus-specific antibodies; neutralization of HIV-1; antigenic variation; IgA and mucosal immunity; immune enhancement.
4. Studies of the correlates of the control of infection and of failure to control: studies of long-term nonprogressors, long-term survivors, rapid progressors, and vaccine

breakthroughs; MHC class I and II regulation of immune response to HIV-1; genetic polymorphisms; role of CD4 and CD8 in infection.

5. Studies of AIDS-related immunology: antigen presentation in infected and uninfected individuals; innate resistance; cellular, humoral, and mucosal immunity; activation and signalling of T and B lymphocytes; cytokines; neuroimmune modulation.

D. Course and Dynamics of Infection/Viral Persistence, Burden, and Reservoirs

With perhaps rare exceptions, HIV-1 is not eradicated by host defenses; large numbers of viral particles in immune complexes remain in lymph nodes associated with follicular dendritic cells (FDCs), and large numbers of infected CD4+ T helper lymphocytes and monocytes/macrophages persist in the lymphoreticular system (LT). Other types of cells, such as thymic epithelia, endothelial cells, and glial elements in the nervous system, may be infected as well. Collectively, virus and infected cells constitute reservoirs from which infection is perpetuated and transmitted and are the root sources of the pathological consequences of infection.

These are not static populations of virus and infected cells but rather, as recent evidence indicates, populations that may turn over in a few days or less. Understanding the dynamics of infection, the size of the reservoir, and the nature of viral-host relationships is at the core of HIV-1 pathogenesis, from the mechanisms of viral persistence and immune depletion, to predicting progression, to disease and outcome. These factors are also a critical measure of the impact of antiviral drugs. Accordingly, the Panel places high priority on the following:

1. Systematic characterization of the numbers and types of cells that HIV-1 infects in the blood and in lymphoid and other tissue compartments, particularly the thymus, bone marrow, gut, and central nervous system (CNS).
2. Systematic quantitative characterization of virus–host cell interactions *in vivo*, in tissues and tissue fluids, to include measures of latent, defective, and productive infections; the relationship of immune activation, cytokines, and other cofactors to productive infection; and estimates of virus associated with FDCs and the impact of that association on FDCs.
3. Dynamic measures of infected cells and virus related to disease progression, outcome, and response to treatment.

E. Immune Dysfunction, Depletion, and Replacement

Dysfunction of the immune system occurs at relatively early stages of infection but it is, of course, the later profound depletion of CD4+ T cells that sets the stage for AIDS-defining OIs and tumors. In the area of etiology and pathogenesis, the mechanisms of immune dysfunction and depletion and failure of the immune system to replace CD4+ T cells is the single most important scientific issue. More specifically:

1. Are dysfunction and depletion mediated directly by infection of CD4+ T cells and, if so, what role do defective and productive infections play? What is the relationship of depletion to viral burden? Is depletion related to the emergence of more pathogenic viruses?
2. Is depletion mediated indirectly by induction of apoptosis, by autoimmune mechanisms, or by superantigens?

On the regenerative side of the equation, there is very little known about or support for research on the human bone marrow–thymus axis responsible for generation of naive CD4+ and CD8+ T lymphocytes whose loss is correlated with AIDS-defining OIs and OTs and about the spread of HIV to these organs. For example, it is not known whether the virus infects stromal elements, accessory cells, and thymic epithelia and, if so, what is the outcome of such an interaction; whether naive cells are replaced by thymic-independent mechanisms or a theoretical third source, the continued renewal of naive cells rather than terminal differentiation into memory or effector cells. Thus, the following critical questions remain:

3. Why doesn't the bone marrow–thymus regenerative system replace T cells lost in infection? Are progenitor cells infected in marrow or in thymus? Are stromal or accessory elements infected? What is the capacity of the adult human immune system to reconstitute naive T cell populations by this axis vis-à-vis peripheral expansion, and what are the functional consequences? Will sustained suppression of viral load by therapy result in reconstitution of a functional immune system?
4. How does infection alter signal transduction, activation, and differentiation of T cells?
5. What role do coinfections with microorganisms, nutrition, other cofactors, and neuroimmunomodulation play in dysfunction and depletion?

F. Cross-Area Issues: Animal Models, OIs, Neuro-AIDS

The manifestations of immune depletion in OIs, OTs, neuro-AIDS, and the involvement of other organ systems, as well as the use of animal models to address the issues raised, do not fall solely within the purview of the Etiology and Pathogenesis Panel. Separate subpanels were therefore created for these cross-cutting issues. Their reports are contained in separate documents.

III. Assessment of the NIH AIDS Research Effort in Etiology and Pathogenesis

A. Recapitulation of the Reviewing Process

The Panel assessed the NIH AIDS research effort, as described in an earlier section of this document, by categorizing the scientific portfolio by priority as (1) relevant and responsive research of high quality; (2) tangential, unresponsive research or research viewed as unlikely to have much impact on understanding pathogenesis; and (3) a large body of work for which there was too little information to be able to assess its quality and potential impact. Table 2 again illustrates the approach. A narrative evaluation of the AIDS programs of the individual ICDs is included in the Appendix. While the Panel fully recognizes that this approach ignores both the historical development of an Institute's portfolio and major problems with the AIDS information systems that may exaggerate the magnitude of poor or inappropriate efforts, the Panel's approach maintains the forward-looking perspective it believes to be essential to improving the AIDS research effort in its area. The approach moreover identifies weaker tangential efforts that must be phased out to free the resources to support more responsive and promising research in etiology and pathogenesis at a time when it is unlikely that these initiatives can be otherwise supported.

B. General Conclusions: High Marks Overall but Ample Room for Improvement

In looking back at research already undertaken and forward at what is underway or planned for the future, the Panel was struck by the impressive scope and responsiveness of the NIH to the scientific issues in etiology and pathogenesis. In just over a decade, the virus that causes AIDS has been identified and a great deal has been learned about the genome, structure, and complexities of the replication of the virus. Extensive and complex programs have been launched, aimed at understanding the natural history and transmission of infection, the immune response to HIV infection, the determinants of progression and outcome, and the pathogenesis of OIs, OTs, and neurological manifestations of HIV-1 infection. Highly qualified investigators have been recruited to the effort.

Partially offsetting this overall praise for the NIH effort, however, is the consistent impression of all of the Panel members that about one-third of the portfolios of the lead Institutes in the area of etiology and pathogenesis (to nearly the entire portfolio in some instances) represents research that the Panel considers to be of dubious quality and relevance. The Panel's overarching recommendation, independent of organizational structure and process, is to bring higher caliber scientists and science to the field, particularly in immunology. This can be achieved only by freeing up resources through elimination of these relatively unproductive programs. Thus, while on balance the Panel's overall positive assessment would not justify radical or revolutionary changes, the Panel is convinced that the NIH must commit itself to the difficult task of identifying and phasing out the research areas that are either less productive, of lesser quality, or of less relevance to contemporary research priorities and redirecting resources from them so that it can reshape and target its programs in etiology and pathogenesis to fulfill the promise of research in the area.

C. Specific Conclusions

Conclusion 1: Human and fiscal resources currently are not optimally focused to answer the critical scientific questions, particularly scientific issues involving human and mucosal immunology.

a. Focus and Emphasis

The in-depth analysis of the etiology and pathogenesis portfolio provides support for the Panel's conclusion that while there are substantial and responsive programs in each priority area, there are also major gaps and major resources directed to programs of dubious quality and relevance.

(i) HIV Genome, Structure, Replication

There are broad-ranging programs in this area, largely supported by NIAID, but the Panel found many instances where research designated as ARR and classified under HIV structure and replication was not truly responsive or likely to have impact. This is particularly the case in the portfolios of NIAAA, NIDA, NIGMS, and NHLBI but applies as well to certain metabolic studies in the NCRR-supported General Clinical Research Centers (GCRCs) and the cancer treatment in cancer centers that are categorized as ARR. Even the leading investment in HIV structure and replication by NIAID, amounting to approximately one-third of its portfolio, is

artificially inflated through the arbitrary designation of a portion of funds devoted to CFARs, cancer centers, and Small Business Innovation Research (SBIR) awards as ARR in etiology and pathogenesis. There are also disparities in productivity, quality, and relevance and levels of support in research programs that fall outside the R01 peer-review system in umbrella mechanisms such as contracts. For example $4-5 million is invested in intramural programs on a low-priority rabbit model (NIAID) and investigations of endogenous retroviruses with no linkage to AIDS research (NCI).

(ii) Transmission, Viral Variation, and Host Defenses at All Stages of Infection

The NIH has supported or currently supports an extensive effort on the transmission of HIV, particularly maternal-fetal transmission, viral variation, entry events, and host defenses. The recent NIAID RFA on sexual-mucosal transmission was especially welcome and overdue, as it addresses this major route of transmission.

The successes and failures of the host defense systems at all stages of infection remain issues of paramount importance that justify the extensive portfolio primarily supported by NIAID. The Panel largely subscribes to the same broad view as this lead Institute on what constitutes ARR but disagrees with supporting as ARR generic projects on antibody structure and diversity; neutrophils and phagocytosis; and B cells, T cells, and antigen-presenting cells (APCs) with no hint of linkage to HIV infection or AIDS. These resources would be much better utilized to support a new emphasis on human immunology.

(iii) Immune Function, Depletion, and Replacement at All Stages of Infection

Despite efforts thus far, we do not understand where or how T cells are depleted and why they are not replaced. Again, the lead Institute in this area, NIAID, clearly understands the critical importance of these issues and has a broad portfolio directed at examining the leading contemporary hypotheses: (1) direct mechanisms involving HIV infection and cytopathicity and (2) indirect mechanisms involving apoptosis, superantigens, and autoimmunity. This is and should be a top priority.

Responsive RFAs have been issued on AIDS and SIV pathogenesis, the consequences of infection in bone marrow, and immune reconstitution. Much more attention needs to be given to this area in a way that will encourage expert immunobiologists to enter the field to find ways of restoring immune function as antiviral treatments improve, or to learn how to create HIV-resistant cells through gene therapy.

There is also considerable support for T cell signaling and activation, which is potentially relevant to the dysfunction in the immune system that accompanies HIV infection. The Panel is aware of concerns that inadequate attention is being paid to nutrition, stress, and neuroimmune modulation and immune destruction; and to cofactors such as mycoplasma in immunopathogenesis. The large portfolio in these areas offers scant evidence to support these concerns. The Panel agrees that the progression of HIV-1 infection and psychosocial factors has not been resolved and that focused, well-constructed studies of the role of neuropeptides and endocrine hormones on immune function and HIV-1 replication are appropriate. There are also ample precedents of the impact of psychosocial factors on the pathogenesis of autoimmune

diseases and viral infections to justify continued studies of psychosocial interventions, life stresses, and coping strategies in disease. In many cases, a majority of the Panel members thought that these studies fall within the purview of the Natural History, Epidemiology, and Prevention Panel and/or the Behavioral, Social Science, and Prevention Panel. Within the scope of its charge, the Panel calls for a definition of ARR that provides a defensible rationale to expect that the investigations will impact our understanding on intervening in HIV infection. Although certain grants listed under psychoneuroimmunology qualify as ARR, the Panel believes that many grants, such as for generic work on opiate receptors or alcohol effects on the immune system supported by NIMH and NIAAA, do not qualify as AIDS research by more rigorous criteria.

b. Funding Mechanisms

In addition to inadequate emphasis on areas of highest scientific priority, inordinate emphasis on areas of lower priority, and research inappropriately classified as AIDS research, the Panel finds that the NIH is not currently employing its resources to maximum advantage to address the major scientific issues in etiology and pathogenesis.

The breadth and complexity of the scientific issues and the urgent need to address them have driven the NIH to make far greater use of funding mechanisms other than the traditional R01 award. This approach has unquestionably been successful in many respects, for example, the interactive program project approach of NIGMS to attract outstanding structural biologists to the field; RFAs issued by NIAID and NICHD on sexual mucosal and maternal–fetal transmission to focus investigations on these pressing issues; and centers supported by NIAID that brought distinguished neuroscientists into the field to work on neuro-AIDS. But as the NIH AIDS program has evolved over the past decade, these approaches have increasingly consumed such a large share of the available resources that the R01 pool is seriously underfunded. The Panel believes that investigator-initiated research continues to be the most responsive and likely route to success in finding a cure and a vaccine and is the best mechanism to attract new investigators to the field.

The R01 mechanism, however, will not in and of itself likely lead to a solution of all the mysteries of HIV pathogenesis, nor is this mechanism without problems. It may turn out to be difficult to recruit high-caliber scientists to work on some critical issues, such as human immunology, because of their complexity or other reasons. In such a case, where there is demonstrable difficulty in focusing attention on a high-priority issue, selective use of RFAs, P01s, or other set-aside mechanisms is justified.

The Panel identified other distortions and problems in funding for research in the area of etiology and pathogenesis. The intramural programs in certain ICDs, particularly in NCI, have consumed a disproportionate share of the resources (approximately one-half). The Panel found throughout the intramural programs other striking examples of the disparity between the quality, productivity, and importance of the research and the resources devoted to it (some of these have been cited previously in this document). Contracts and centers have still other problems related to timing and open competition for resources. The Panel believes that major investments, for example, in the immune correlates of infection, need to more closely coincide with scientific opportunities such as a vaccine efficacy trial. The Panel believes that the

playing field needs to be more level in the competition for resources and sees the RPRCs, for example, as largely a "closed shop" with relatively little access to this critical resource by outside investigators. Similarly, centers can be sound investments, and program staff have and will play important roles in recruiting scientific talent to focus on critical areas through the center, RFA, and other mechanisms. However, it is now time to reconsider both investment strategies and process. The large financial commitment in centers (for example, by NIMH) must be reexamined for productivity and impact on neuro-AIDS and weighed against what potential the same resources might have if they were used to attract new scientific talent to the field.

Conclusion 2: There are currently serious problems with AIDS peer review and AIDS information systems.

The Panel strongly believes that the objectives of the peer-review process — to identify and direct resources through open competition to the most qualified scientists to conduct discovery research — have in some instances been seriously compromised and that this accounts for many of the problems in the portfolio and disincentives to attracting the new and distinguished investigators the field needs. To identify the most deserving innovative and excellent proposals, there can be no substitute for exceptionally well-informed, high-caliber scientists on study sections with the expertise and objectivity to make these judgments. What the Panel heard, however, from DRG representatives was an inordinate emphasis on ethnic, geographic, and gender diversity at the expense of expertise. In addition, the lines of communication are poor between study sections and the advisory councils involved in funding research, NIH and OAR program staff, coordinating committees, and workshop participants who are trying to set the research agenda. It is, therefore, no great surprise that the portfolio and priorities are disconnected in many instances. In addition, the current peer-review process is unlikely to bring new talent to the field to work on long-range projects, given the focus on preliminary data rather than track record, and the generally poor and short-term funding prospects.

The second problem with peer review at present is that it is not sufficiently encompassing. Review and assessment need to be applied with equal force to all forms of NIH support, including intramural research, contracts, cooperative agreements, and centers. The Panel also heard reports from study section members of redirection of resources apparently largely by Institute staff, thus bypassing the intent of the peer-review process altogether.

The third problem with peer review and the whole issue of accountability is the current information-retrieval system. The Panel was forced to go to inordinate lengths to retrieve and organize information on what etiology and pathogenesis research the NIH supports and to accurately account for what it spends. Part of the difficulty stems from how ARR is defined. The Panel recommends moving from the present oftentimes arbitrary and idiosyncratic designations to a rigorous evolving definition that is the product of discussions between the ICDs, OAR, and scientific working groups. The Panel's principal recommendation in this area, however, is for development of an up-to-date electronic information system that properly categorizes research in the portfolio and correctly associates the actual dollars spent on the project. Such a system is essential to monitor the effectiveness of the programs vis-à-vis the resources dedicated to them.

Conclusion 3: There is currently inadequate access to and use of two critical resources: animal models and tissue repositories.

Animal models are a precious resource, not just to answer questions of an individual investigator but as a shared resource for the scientific community. This is particularly the case for nonhuman primates, which are critical for studies of immunity and pathogenesis, for evaluating genetically engineered changes in the viral genome, and for development and testing of drugs and vaccines. While the ungulate models, FIV, HuSCID, and transgenic models will continue to be useful for some issues of pathogenesis, the primate model and the RPRCs are of preeminent importance. These centers, and the resources NCRR devotes to them, are largely utilized by permanent staff at the centers. As a consequence, access to and use of the primate model by scientists outside the centers is far too limited, and the competition for this vital resource is not sufficiently open or appropriately peer reviewed. In view of the limited utility of chimpanzees for studies of AIDS pathogenesis, resources currently set aside for breeding and maintaining chimpanzees would be better utilized by NCRR for openly competed studies in macaques, once an alternative mechanism of support for the chimpanzee expenses is defined.

In the area of etiology and pathogenesis, repositories of molecular and immunological reagents and banks of tissue samples generated in cohort studies are critical and limited resources and the raw materials for all aspects of studies of pathogenesis directed to understanding interactions between HIV and its human host. The Division of AIDS (DAIDS) of NIAID has developed state-of-the-art centralized systems to collect, catalog, store, and distribute reagents, tissues, and body fluids from cohorts that include the Multicenter AIDS Cohort Study (MACS), Women and Infants Transmission of HIV Study (WITS), Women's Interagency HIV Study (WIHS), HIV Vaccine Efficacy Trials Network (HIVNET), AIDS Clinical Trials Group (ACTG), AIDS Vaccine Evaluation Group (AVEG), and Division of AIDS Treatment Research Initiative (DATRI). The Panel views the reagent repository as a success story and model and acknowledges as well the valuable contributions to date of the specimen repository. Greater benefit, however, could be derived from the repositories, for both individual research programs and collaborations between clinical and basic scientists, by better collection and distribution of specimens, guided and driven by research questions and in accord with a philosophy of open access to all qualified investigators.

The Panel was in general agreement with other guidelines for the sample repositories under consideration at NIAID, such as evaluation of requests by scientific merit; first rights for fulfilling predetermined purposes of a research protocol for which the specimens were collected; treating specimens as a scarce and valuable resource and accordingly limiting the size of a request; barring sale of specimens or use for commercial purposes; maintaining patient confidentiality; and safe handling of specimens.

IV. Recommendations

A. General: engage the best scientific talent in the formidable quest to solve the mysteries of HIV pathogenesis

This transcendent recommendation, to retain and recruit scientific talent in a truly focused effort to address the issues of highest scientific priority, translates into specific

recommendations on focus and emphasis, resource utilization, improved peer review, information systems, use of animal models and tissue repositories, and organization and process.

B. Specific Recommendations

1. Improve funding for unsolicited investigator-initiated research but maintain balance and appropriate emphasis through selective use of other funding mechanisms.

There was a resounding consensus that the R01 pool of funds currently is simply insufficient and that this mechanism generally has been and will continue to be the best mechanism to address the outstanding scientific issues and to attract new junior and senior investigators from other fields to AIDS research. The Panel therefore recommends that:

1a. The support for unsolicited investigator-initiated AIDS research be doubled to provide the incentives and resources to attract outstanding investigators and fund meritorious projects.

The Panel also sees a need for the selective use of other mechanisms of funding and for long-term stable support to maintain focus and balance in the portfolio, move in new directions, and encourage innovative research with long-range objectives. When the R01 mechanism demonstrably fails to stimulate high-quality science in areas of high priority, the Panel recommends that:

1b. RFAs with set-aside funding be used selectively, both to focus attention on important areas of pathogenesis research and to bring established or new high-caliber scientists into the field.

This recommendation arose out of discussions of critical shortcomings in our understanding of human immunology and mucosal immunity and of two superficially disparate examples of how successful programs in AIDS etiology and pathogenesis research had been initiated in the past. The first of these is a program, initiated by the director of NIGMS, on the structural biology of HIV that brought together distinguished investigators for work funded by well-organized interactive program project grants. The second program, an RFA with set-aside funding issued by NIAID, reflects in large measure NIAID's response to previous reviews of the pathogenesis agenda in 1993 calling for substantially increased efforts to understand sexual mucosal transmission of infection. What these programs have in common are:

- Enlightened and well-informed NIH staff working with the extramural scientific community through personal contacts, program reviews, workshops, and conferences to identify important areas of research;

- Involvement of the non-Government scientific community in formulating and disseminating the announcement of the initiative in a way that encourages scientists from other fields to apply and consortial (“dream team”) approaches by collaborating investigators from different institutions/sectors;

- Set-aside funding.

2. Enhance the emphasis on long-range discovery research in areas of highest priority, especially human immunology.

Another recurring theme in the Panel's discussions was why more exceptionally distinguished scientists are not actively involved in AIDS pathogenesis research and why a relative paucity of really first-rate projects have been directed at the central issues. In the Panel's analysis, the problem in large measure stems from the lack of long-term support and other incentives to encourage distinguished scientists to undertake innovative high-risk but high-payoff discovery research of the kind sponsored by HHMI, for example. Greater use of Merit awards, supplemental funding for senior investigators, and joint R01s are some ways the NIH might encourage innovative research.

2a. Use Merit and similar awards (e.g., Javits awards) and devise incentives to encourage long-range and innovative research.

The Panel believes that the high-caliber, exceptionally creative immunologists and many aspects of HIV/SIV immunology are underrepresented. To draw talented immunologists not now involved in AIDS research into the field, the Panel recommends that OAR and the NIH should:

2b. Convene a series of meetings of expert non-AIDS and HIV/SIV immunologists to consider ways of engaging immunologists in the effort to address the critical issues;

2c. Provide supplemental funding to attract senior immunologists into the field; and

2d. Establish consortial approaches between basic immunologists and investigators currently engaged in AIDS research. The anticipated benefits of the consortial approaches include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows will go into AIDS research.

Where will the resources come from to accomplish these goals? One major source, identified previously in this report, is funds that can and should be redirected from programs in the portfolio classified by the Panel as (1) irrelevant, (2) of dubious quality, or (3) of indeterminate nature or quality (e.g., generically described awards to fund centers, contracts, cooperative agreements, or intramural programs). Moreover, rigorous guidelines for what constitutes AIDS research and ARR likely to impact the epidemic can also free up needed resources (see below). Improved peer review and opening competition to all funding sources are other potential sources. Lastly, some of the monies currently expended under the category of etiology and pathogenesis research within the ACTGs, statistical centers, and the NCRR, but which are currently used for general biomedical infrastructure support, might have greater impact if they were, in fact, used to support basic research on HIV pathogenesis. OAR should establish a mechanism involving the non-Government scientific community, such as the annual scientific planning workshops, where there is open discussion and decision making on the portion of the

AIDS research budget designated currently as pathogenesis that should be used to support the general costs of biomedical research and AIDS research.

3. Improve peer review, quality control, and AIDS focus.

The Panel's conclusions that a substantial portion of the portfolio is of disappointing impact and relevance and that there are many examples of a closed-shop mentality in the use of some of the resources immediately implies the need for improved peer review, AIDS focus, and open competition. The Panel makes the following recommendations:

3a. Institute open competition for funding from all sources: grants, contracts, cooperative agreements, centers.

3b. Use comparable criteria across the board in evaluations of intramural and extramural research. The principal criterion for assessment must be the quality of science and scientists, and the focus and potential impact on AIDS. Emphasis in the review, however, may need to be different to attract investigators to investigate the human immune system. For senior investigators, the emphasis should be on merit and track record, whereas for junior investigators the emphasis should continue to be the strength of the proposal and preliminary data.

3c. Examine all NIH research funding on a regular basis by reviewing bodies with a majority of non-Government extramural scientists. All reviewers should be chosen by their record of scientific accomplishment and productivity and knowledge of the field relevant to the review.

3d. Improve peer review. Paramount consideration in peer review must be scientific expertise demonstrable by previous accomplishments, productivity, and knowledge of the area under review. The status quo will likely be maintained if better scientific reviewers are not engaged in the peer-review process. The Panel recommends the following mechanisms to improve peer review:

- Identifying scientists with expertise appropriate to the review by working with research societies, and
- Using roving *ad hoc* members freely and exercising flexibility in diversity and gender in study sections, as needed, to ensure reviewers with appropriate expertise.

3e. Improve AIDS Focus

Peer review also needs to be reconnected to scientific priorities through better communication between DRG and program staff and the OAR and ICDs, and between study sections and OAR and ICDs. The Panel endorses a recommendation in the Cassman Report on DRG to create a peer-review oversight group (PROG). The Panel recommends that PROGs be created for both intramural and extramural NIH research and that OAR participate with the PROGs in AIDS-related reviews. OAR should also have disparate and parallel input to the final evaluation/ranking of the review panel and, following council review, final funding decisions should be made by the Institute Director in consultation with the Director of OAR.

4. Formulate and implement mechanisms to increase access and improve the use of critical animal model resources and specimen repositories.

Animal models. Access to the primate model and the RPRCs must be facilitated and the review of the centers and investigators improved by:

4a. Competition for AIDS research project funding by NCRR should be opened to all non-Center investigators, rather than only to permanent RPRC staff.

4b. NCRR study sections that review the RPRCs should incorporate expertise in AIDS and ARR.

4c. There should also be open competition for animal cost-funding of DRG-reviewed grants through a regularly recurring RFA.

4d. Given the limited utility of the chimpanzee model for HIV pathogenesis studies, additional funding for promising studies in other models (particularly SIV-infected macaques) should be derived as well by redirecting monies currently expended in the less relevant chimpanzee model.

Specimens. Qualified investigators need better access to appropriate tissue specimens and fluids. The Panel recommends greater collaboration between clinical and basic researchers and program staff in determining the type of sample needed and frequency of collecting and sharing these previous resources on the basis of scientific priority and merit.

4e. The OAR, in conjunction with the ICDs and non-Government scientific community, should establish NIH-wide guidelines for access to clinical samples.

- The type and frequency of samples collected should be appropriate to the investigation. This is a moving target that will require an explicit mechanism to ensure interaction between investigators, clinicians, and those responsible for the repository to decide what should be collected and priorities for distribution.

- Qualified investigators must have better access to samples. Guidelines currently being developed (e.g., at NIAID) should convey a sense of public ownership and should separate collection of samples from access to samples by all qualified investigators.

The tissue repository should be seen as an exceptional opportunity to engage clinicians and basic scientists in the discovery of key aspects of HIV pathogenesis, and to link basic and clinical investigators in collaborative efforts.

5. Define and focus the scientific portfolio of AIDS and AIDS-related research and associated program resources.

To align scientific priorities with programs and resources, the NIH needs to develop better information systems and be able to properly identify resources that are appropriately designated AIDS or AIDS-related research (ARR). The Panel recommends that the NIH and OAR:

5a. Develop a new AIDS information system that: lists grant titles and numbers, investigators' names and institutions, dollar amounts, funding ICDs, and abstracts; is searchable by these parameters and by topic area (e.g., MESH headings); lists publications stemming from the research; can be applied equally to all NIH-funded AIDS research; and is user-friendly and accessible to all those involved in the evaluation of NIH-funded AIDS research.

5b. Establish mechanisms to appropriately define ARR that: are broad but rigorous; are consistent across all NIH ICDs; and involve the non-Government research community in an ongoing decision making process.

The Panel is insistent that there be an explicit defensible rationale to define ARR and a process for redefining ARR as scientific progress reveals new areas of relevance. The Panel also recommends that the resources devoted to ARR be clearly identified on a reasonable rather than arbitrary basis. For example, 5 percent of ACTU budgets currently are designated as pathogenesis-related whether or not these funds are used to support research in this area. The Panel supports a broad definition of ARR but asks for an explicit rationale linked to the scientific issues and strategies. Defining ARR should be a conjoint effort of the ICDs and OAR, perhaps best carried out through established mechanisms of discussions at the ICDs, coordinating committees, and OAR workshops. Because AIDS relevance is a moving target, definitions should be updated annually or semiannually. Research proposals should be predesignated by the PI as AIDS or ARR and reviewed by appropriate panels that include OAR staff.

6. Strengthen OAR's role in etiology and pathogenesis research.

If not obvious at the outset, it certainly became clear to the Panel in the course of its assessment that OAR is essential to coordinate the NIH's effort in AIDS etiology and pathogenesis. The Panel's recommendations include the following:

6a. OAR should set the scientific agenda and priorities in a collaborative effort with the directors of the ICDs, coordinating committees, working groups, councils, advisory bodies, non-Government researchers, and community representatives. To better communicate scientific priorities, relevant study section chairs should be included in the process of setting the OAR scientific agenda.

6b. OAR should align high-caliber scientists and science with the priorities and resources by having and exercising fiduciary control and responsibility for all NIH AIDS research. This would include intramural research, contracts, and cooperative agreements as well as new and competing extramural support.

6c. OAR and the ICDs should continue to regularly and systematically solicit advice from leading Government and non-Government clinical and basic investigators in the formulation and plans for etiology and pathogenesis research.

V. Animal Model Subpanel Report

A. Background

Animal models have proven to be of central importance in investigating the pathogenesis of lentivirus infections. Equine infectious anemia was the first animal disease recognized to be caused by a virus. Other ungulate lentiviral infections, including maedi-visna virus infection of sheep, caprine arthritis-encephalitis virus infection of goats, and bovine immunodeficiency virus infection of cattle have also been extensively studied. Pioneering observations made in these studies have included the first demonstration that persistent lentivirus infection can occur with restricted viral replication and slow progression of disease; macrophages can act as an important target cell and virus reservoir; progressive antigenic change of the viral surface glycoprotein can occur; and maternal transmission of virus can occur through colostrum. These studies set the stage for subsequent studies of HIV when it was identified as the cause of AIDS many years later. Feline immunodeficiency virus (FIV) infection of cats may also be useful for specific studies of lentivirus pathogenesis.

The most intensively studied animal models for evaluating human lentiviral pathogenesis have been the immunodeficiency virus infections of higher primates. These infections include HIV-1, simian immunodeficiency virus (SIV), HIV-2, and chimeric simian human immunodeficiency virus (SHIV) infections of macaques, and HIV-1 infection of chimpanzees. The unequivocal demonstration that primate immunodeficiency viruses cause AIDS was made in the SIV/macaque model. Moreover, the roles of auxiliary genes in lentiviral pathogenicity have been demonstrated in this model. Finally, the precise immunopathogenic events occurring during primary infection have been illustrated in SIV-infected macaques.

Small animal models have also been used in studying AIDS pathogenesis. These models include humanized SCID mice (created either through human lymphocyte or through human fetal thymus and liver or lymph node grafting), and transgenic mice and rabbits.

There have, however, been some disappointments in AIDS animal model development. Foremost among these disappointments is the clear evidence now that HIV-1 itself does not reproducibly cause an AIDS-like illness in any primate species. Furthermore, the small animal models that have been explored have had a more restricted utility than was initially hoped. Nevertheless, many central questions in AIDS pathogenesis can be answered only through intensive study in carefully selected animal models of lentivirus infection.

Scientific Priorities for Future Studies

Many issues in AIDS pathogenesis can best be clarified in animal models. The definition of the immunobiology and virology of mucosally initiated infections can be accomplished in an experimental setting in animal models where the strain of virus, dose, route, and timing of infection can be controlled. Only in animal models can the immune system be selectively manipulated to allow a definition of the components of the immune response important for control of virus replication and spread of infection. The life span of immune cells and their regenerative capacity can best be determined in laboratory animals. Animal models will be crucial for clarifying the mechanisms responsible for rapid clinical progression or long-term

clinical stability in lentivirus-infected individuals. Finally, it will be important to employ animals to explore the molecular determinants of virus virulence and tropism.

Many of these issues will best be addressed in a manner most relevant to HIV infections in man through studies in nonhuman primate models. SIV-, HIV-2-, and SHIV-infected macaques will prove central in addressing these issues. The absence of reproducible pathogenic consequences in macaques and HIV-1-infected chimpanzees (as well as the expense of this model and the ethical constraints on research involving chimpanzees) has made these particular models of limited value in studying AIDS pathogenesis. While ungulate and feline lentiviral infection models will be useful to provide comparative information on pathogenesis of these infections in their natural hosts and may provide new insights into lentivirus pathogenesis, they are likely to prove less powerful than the primate models for AIDS-specific issues. Selected questions of relevance to human disease pathogenesis will continue to be usefully addressed in the humanized SCID and transgenic mouse models. The rabbit models have, to date, been disappointing.

AIDS Pathogenesis Animal Models Research Currently Supported by Individual Institutes and Centers

There is considerable variability in quality and relevancy to AIDS in the studies supported by the Institutes and Centers. The mechanisms through which this money is distributed also vary widely. Much of this work is not open to competition in a way that ensures that the best science is funded for the dollars spent. For instance, the animal model work supported by NICHD is appropriately focused on the sexual transmission of HIV and on neonatal infections, but the funding of these primate studies is through cooperative agreements with a limited number of hand-selected investigators rather than through open, peer-reviewed competition. NIMH directs a significant proportion of its animal models pathogenesis funds to selected centers that do not appear to be seriously exploring the most pressing AIDS-related issues. Much of the intramural and extramural work in AIDS funded by NIMH appears to be directed centrally from the program and not open to real competition.

NCRR derives 40 percent of its Regional Primate Research Centers (RPRC) budget from AIDS funding. The competition for the portion of these funds available to support research (as opposed to infrastructure) is open only to full-time RPRC investigators. By restricting the competition for this funding to a very limited pool of investigators, many laboratories well qualified for doing AIDS pathogenesis studies in nonhuman primates may be unable to support these expensive studies through R01 funding mechanisms. NCRR should support nonhuman primate AIDS-related studies by distributing these AIDS funds through regularly recurring RFAs open to all non-Government investigators and through funding the animal costs of DRG-reviewed R01s. Approximately $6 million per year is spent to support the maintenance of chimpanzees for potential AIDS research uses. However, considering the expense and limitations of chimpanzee models and the emergence of SHIV models in macaques, it is difficult to argue for a continued large expenditure of funds by NCRR for maintaining chimpanzees and chimpanzee-breeding facilities.

While substantial AIDS pathogenesis animal models funding has come from NCI, it has proven difficult to determine precisely how that money is currently being spent. NIAID has maintained

a significant commitment to the elucidation of AIDS pathogenesis with open competition for grants and contracts. Substantial progress has been made through NIAID-supported AIDS animal model studies to clarify AIDS pathogenesis. In this as well as the other Institutes and Centers, it would be helpful to rationalize the decisions made as to how much funding in AIDS animal models pathogenesis research should be directed within the NIH and how much should be directed outside the NIH. The mechanisms employed to make funding decisions on marginally useful projects proposed in response to selected RFAs by NIAID might also be clarified.

Recommendation

With a certainty that animal models will continue to be important in the future for studying AIDS pathogenesis, continued support for animal model research is warranted. A broadly based portfolio that supports research into natural lentiviral infections of many species is encouraged. For focused AIDS-specific questions, emphasis should be placed on nonhuman primate models in which AIDS occurs. Murine systems will be useful for restricted purposes. Funding mechanisms that bypass true, open competition for funds should be eliminated. If an Institute is not in a position to oversee open competition for the funds, these funds should be dispensed to other Institutes.

VI. Neuropathogenesis Subpanel Report

A. Background

One of the most prominent and dreaded manifestations of HIV infection is neuro-AIDS because of its profound impact on the cognitive and emotional lives of afflicted children and adults. How and when does HIV enter the nervous system to cause this affliction? How does infection cause the cellular and systemic injuries underlying neurobehavioral impairments? Why do some people develop this complication while others with similar viral burden and degree of immunosuppression do not? Is the brain a sanctuary for the virus and a reservoir to perpetuate infection? And, most important, what kinds of treatments will specifically reach the nervous system to prevent or ameliorate the effects of an infection that, in the aggregate, constitute the greatest epidemic affecting the human nervous system in recorded history?

These major questions define the issues in the neuropathogenesis of HIV infection that were considered by the Neuropathogenesis Subpanel, made up of members of the Etiology and Pathogenesis Area Review Panel and the Behavioral, Social Science, and Prevention Area Review Panel. The summary that follows sets forth (1) the scientific issues the Subpanel considered to be of highest priority; (2) an assessment of current NIH-wide activities to address these issues; and (3) recommendations for the future to initiate or redirect efforts to more effectively grapple with these challenging questions.

B. Scientific Priorities

There is general agreement between the Subpanel's conclusions and those reached in recent analyses by ICDs, OAR, and the Institute of Medicine (IOM) that the most important, outstanding scientific issues in neuro-AIDS at present are:

- Understanding how viral infection contributes to nervous system impairment through direct interactions of HIV with neuronal and non-neuronal cells and indirect mechanisms, in particular, those mediated by cytokines and neurotoxins elicited by the infection or the immune response to infection.

- Determining how and when HIV enters and how the virus persists in the nervous system. Questions include:

    - Whether neuroinvasive/neurovirulent strains of HIV are responsible for neuro-AIDS;
    - The time of entry vis-à-vis viral burden in the periphery and immune impairment;
    - The role of inflammation, macrophages, endothelial cells, and alterations in the blood-brain barrier in entry and injury;
    - The role of host defenses operating in the nervous system in viral clearance, persistence, and injury at different stages of the systemic infection; and
    - The role of the nervous system as a virus reservoir and protected environment from antiviral drugs and host immunity.

- Assessing the impact of psychosocial and environmental factors on the development, course, and severity of neuro-AIDS mediated by neuroimmune modulatory mechanisms.

- Developing the neuropsychological assessment and neuroimaging tools to measure and monitor neurobehavioral impairments and determine the structural correlates underlying dysfunction.

The Subpanel ranked these issues so highly because their resolution will provide the foundation for development of new strategies and agents to prevent and treat HIV-associated neurological disease.

Status Report

The detailed review of the NIH extra- and intramural portfolio relevant to neuro-AIDS and testimony of program directors and staff in the leading Institutes, NIMH and NINDS, provided the Subpanel with evidence of the scope of the efforts and the appropriate urgency of the response. By a variety of mechanisms, ranging from traditional R01 grants to program projects and the establishment of centers, the ICDs have engaged leading investigators and encouraged, solicited, and sponsored research aimed at answering the questions the Subpanel thinks deserve emphasis. A substantive body of work is focused on neurotropism and neurovirulence, entry of HIV into the nervous system, and the interplay between host defenses in the nervous system, viral replication, and persistence. Leading contemporary hypotheses about the mechanisms of injury to the nervous system caused by inflammation, cytokines, and the toxic effects of viral proteins are being explored, and individual investigators and consortia are being supported to develop and apply methods to assess and characterize the neurobehavioral manifestations of HIV infection in adults and in children. Many of the central issues of neuropathogenesis are being addressed in a variety of animal models, from ungulate and feline lentiviral infections to murine and transgenic models and the nonhuman primate models that the Subpanel consider the most relevant, albeit expensive, model.

NIMH, NIDA, and NIAAA also support as AIDS-related research a variety of projects of a more general nature focused on alcohol, opioid, and other drug effects in the nervous system and mechanisms of neuronal toxicity, e.g., mediated by nitric oxide. The rationale for the inclusion of these investigations in the neuropathogenesis portfolio is evidently also generic, so that a true understanding of the pathogenesis of AIDS dementia complex (ADC) may come from discoveries made in ostensibly unrelated areas.

Opportunities, Recommendations, and Strategies

The Subpanel on the whole was impressed with the quality of the science and the scientists who are devoting their attention to the neuro-AIDS problem and to the comprehensiveness of the portfolio. Nonetheless, progress in basic research in this area has proceeded at a relatively slow pace, and basic research findings have yet to be meaningfully translated into clinical applications. There are clearly outstanding issues that remain unresolved and a need to commit and recommit to the opportunities—scientific opportunities, opportunities to attract more qualified scientists to the field, and opportunities to improve the depth, focus, and coordination of the NIH's response to combatting neuro-AIDS. To fulfill the promise of neuropathogenesis research to devise better means to prevent and treat neuro-AIDS, the Subpanel reiterates its view that there are continuing opportunities for research on:

- Viral entry, the early stages of infection of the nervous system, and the timing, course, and severity of impairments;
- The morphological, biochemical, and molecular bases of neuronal dysfunction;
- Increased emphasis on *in vivo* models of neuropathogenesis, particularly HIV-infected humans and SIV-infected nonhuman primates; and
- Better integration of basic research studies of the neurologic complications of AIDS with ongoing natural history studies and clinical trials, particularly studies of antiviral drugs that might affect the incidence or manifestations of neurologic complications by altering levels of HIV replication *in vivo*.

How will more talented scientists be recruited to address these issues, and where will the resources come from to support their efforts as well as the high-quality focused programs in place? The Subpanel believes from its in-depth review that much can be accomplished through coordination facilitated by OAR and by better use of existing resources.

Recommendations

- **OAR should coordinate all efforts directed at neuro-AIDS across the NIH in all intramural and extramural programs, and by all mechanisms, to align the research programs with the scientific priorities. The RFA on the blood brain barrier and neuro-AIDS jointly issued by NIMH and NINDS and workshops on neuro-AIDS cosponsored by NIMH, NINDS, and NIAID provide recent and past examples of fruitful cooperative ventures and a paradigm for the future, for both research and training.**

OAR's role is to facilitate and enhance coordinated efforts, and to do so it must put in place improved information and electronic communication systems that are accessible and user-friendly. With the current database, the Subpanel found it difficult to evaluate the correspondence between OAR scientific priorities and the research portfolio, and between the research portfolio in neuro-AIDS and the listed resources. To fulfill its mandates of coordination and accountability, OAR must remedy these problems but, on a larger scale, the NIH and research community must have better ways to learn about scientific opportunities and collaborations, and the ICDs must be better positioned to link programs and investigators to focus attention on scientific priorities.

- **Substantial support for research the Subpanel views as highly relevant and likely to impact greatly on neuro-AIDS can be generated by redirecting and refocusing resources, using existing mechanisms that involve OAR, the NIH, and non-Government scientific communities. The coordinating committees and annual OAR workshops define and redefine scientific priorities and ARR. These definitions should be used to align programs and resources and to replace current practices in research that is tangentially related to neuro-AIDS or apparently unrelated but important to neuroscience and that might eventually prove related (such as work on opiate receptors) is classified as ARR. This work should be supported on its own merits and not as ARR. Similarly, practices of arbitrarily assigning funding as neuro-AIDS, e.g., in ACTUs, should be discontinued in favor of rigorous and explicit rationales for designating funding as neuro-AIDS.**

- **Shared resources are critical to the success of understanding the pathogenesis of neuro-AIDS. These resources include the primate centers, designated centers for neuro-AIDS research, and tissue repositories essential for research with *in vivo* relevance. The Subpanel endorses the conclusions of a number of the Area Review Panels that access to the primate and transgenic murine models must be improved. The Subpanel also supports efforts to improve centralized systems to collect, catalog, and distribute reagents and tissue specimens and the involvement of the scientific community in determining the type and frequency of sample collection.**

Conclusions

In seeking ways to prevent and treat the mental and emotional suffering of neuro-AIDS, there is a broad scientific consensus that we must understand how and when HIV enters the nervous system and how it causes injury. In reviewing the NIH's progress and plans to answer these questions and to address the transcendent issues of the mechanisms of injury to the nervous system caused by infection, the plasticity of the nervous system in recovery, and the interactions between the nervous and immune systems, the Subpanel found much to praise in the breadth and pace of the response in the lead Institutes, NIMH and NINDS. The Subpanel's recommendations focus on how to enhance these efforts by engaging new scientific talent, coordinating the effort across the NIH, and facilitating access to critical resources. The Subpanel specifically recommends:

- Better coordination by OAR of all NIH-supported neuro-AIDS research and training. This will require improved information and communication systems.

- Improved alignment of research programs with scientific priorities. This linkage can be strengthened by fully utilizing extant mechanisms sponsored by OAR, such as NIH-wide coordinating committees and annual workshops to identify and prioritize scientific issues and research likely to have the greatest impact. This evolving and open approach to defining ARR should replace current less-rigorous practices and rationales.

- Primate centers, neuro-AIDS centers, and repositories of reagents and tissue samples represent critical resources that must be more widely shared. The Subpanel supports mechanisms to accomplish this described in detail in the reports of the Etiology and Pathogenesis Panel and the Behavioral, Social Science, and Prevention Panel.

Appendix A

Review of Institute and Center HIV/AIDS-Related Programs

NIAID

NIAID's contributions to advancing knowledge about the etiology and pathogenesis of HIV and HIV disease have largely been a success story. Studies conducted by both NIAID-supported extramural and intramural scientists have helped define essential aspects of the biology of HIV and yielded important insights into the pathogenesis of AIDS. In reviewing the entire NIAID effort in AIDS Etiology and Pathogenesis research, the Panel finds that a number of programs deserve particular praise, some where improvements should be made, and others where efforts were found to be insufficiently productive or relevant and should be improved or discontinued.

The NIAID intramural program in Etiology and Pathogenesis research includes some of the world's leading investigators in the area, and the Panel acknowledges the exceptionally important contributions that they have made to the field. However, the Panel also came to appreciate that the quality of the NIAID intramural program is uneven, and that a number of investigators supported by AIDS research funds have pursued studies that have little direct relevance to AIDS or that have produced few new insights. The Panel was also struck by the high level of funding provided to certain intramural laboratories relative to their productivity. It believes that optimization of the quality of the intramural program would be enhanced through more rigorous external review, as described elsewhere in this report. Further, the Panel believes that support should be commensurate for equally qualified intramural and extramural scientists.

The portfolio of extramural research supported by NIAID is very large and diverse, and a number of distinct funding mechanisms are used to support these efforts. In general, the Panel believes that this work has been very productive and appropriately focused on important topics in AIDS. Further, the Panel was impressed by the commitment of the NIAID program staff to supporting and facilitating innovative, high-quality research on AIDS pathogenesis. However, the Panel also believes that there are specific areas and programs that could be improved substantially. As discussed elsewhere, the Panel is concerned about the level of funds provided through contract mechanisms by DAIDS staff; the research these funds support appears to be subject to limited rigorous scientific review. It is the Panel's view that external scientific input should be solicited during the planning stages of any such contract activities.

A number of NIAID initiatives deserve specific comment:

- The AIDS Research Reference Reagent Program has served an extremely valuable role in facilitating the entry of new investigators into AIDS research and clearly should be continued and expanded as necessary.

- The HIV Sequence Database, funded by NIAID through an interagency agreement with the U.S. Department of Energy, represents an invaluable resource for the AIDS research community. NIAID is to be congratulated for its foresight in supporting development of this database and its continuing commitment to it.

- The Center for AIDS Research (CFAR) program has functioned in a very productive manner in some locations, whereas other sites have been significantly less productive. The Panel is aware of the commitment of the DAIDS staff to maximizing the quality of all funded Centers but found the recent decision to decrease external review of each of the individual Centers (by an external advisory board) in favor of what is essentially a self-review process runs counter to this goal. The Panel believes that the more productive Centers should be provided with increased resources, while the less productive Centers should be improved or, if this is not possible, eliminated.

- NIAID supports a number of studies of the epidemiology and/or natural history of HIV infection, including MACS, WIHS, WITS, and HIVNET. Such studies, when appropriately structured and conducted, can provide critically important opportunities to learn about the basic biology of HIV and the disease it causes. Certain studies, such as MACS, have a record of significant contribution to this area and have recently provided key specimens and data that illuminate the role that the level of HIV replication plays in determining the rate of progression to AIDS following initial infection. WITS, which focuses on elucidation of the determinants of maternal-fetal transmission of HIV, has been less productive. WITS was begun in 1988 (and entered the field in 1989), but it was not until 1993 that the first peer-reviewed publication appeared. Recent WITS results concerning the relationship between maternal virus load as a potential determinant of risk of perinatal HIV transmission are important; however, the Panel is concerned about the relatively slow pace of data acquisition, analysis, and publication by WITS investigators. The WIHS project investigation of HIV infection in women is the most recent large natural history study to be initiated, and it is too early to fairly assess its productivity. However, the Panel is concerned that this study already displays characteristics that have limited the productivity of other similar studies in the past, including internal disputes among study investigators, incompletely defined procedures for clinical sample collection and distribution, lack of external input by expert HIV virologists and immunologists, and a diffusely defined basic research agenda. In all of these studies, the Panel believes that the ability of a natural history study to contribute to our understanding of the pathogenesis of HIV disease will be best accomplished by hypothesis-driven investigations that are collaboratively designed and conducted by expert epidemiologists, clinicians, and basic HIV virologists and immunologists. Input from all of these sources of expertise should be obtained at the initiation of all studies, and expert external oversight should be exerted throughout their course.

- The Correlates of HIV Immune Protection (CHIP) laboratory contract funded by NIAID was awarded in 1994 to support studies of the correlates of immune protection gleaned from anticipated Phase III studies of candidate HIV vaccines. However, as no Phase III studies have yet to be initiated, the current goal of this contract has become less clear. As discussed elsewhere in this report, illumination of the correlates of immune protection is an essential research need. However, at this juncture, research on this topic might best be fostered through traditional R01 or, potentially, U01 mechanisms. As recommended elsewhere in this report, the HIVNET program should be reviewed to determine its most appropriate scope and mission in the absence of a clear plan to conduct Phase III vaccine efficacy studies in the near future. The CHIP contract might be similarly evaluated at that time.

- NIAID also sponsors a number of clinical trials programs, and these represent critically important opportunities to learn about HIV virology and pathogenesis. These programs include the Adult and Pediatric ACTGs (cofunded by NIAID and NICHD), CPCRA, DATRI, and SPIRAT. The Adult ACTG has made significant contributions to advancing the treatment of HIV infection and its complications and has gleaned important experience with the use of virologic assays to monitor HIV infection *in vivo*. However, given the enormous potential for learning about HIV pathogenesis from interventional drug trials, the Adult ACTG has not been on the vanguard of this effort. The Panel is aware that the Adult ACTG has recently formed a Scientific Advisory Board comprised of scientists from outside the ACTG. We encourage this Board to work with the leadership of the ACTG and the DAIDS staff to define the appropriate future role for the ACTG in this area. In addition, efforts should be made to provide non-ACTG investigators with access to clinical samples obtained in the course of ACTG studies, as well as improved opportunities to participate in the initiation and design of new studies. The ACTG should not be a "closed shop." To the Panel's knowledge, the CPCRA has not yet established meaningful linkages with basic research scientists investigating the biology of HIV infection and its complications (e.g., OIs and malignancies). We encourage the CPCRA leadership and DAIDS staff to consider ways of utilizing the large clinical population followed by this network for basic research investigations. The Panel believes that the DATRI program has largely failed to take advantage of its potential to gain new insights into HIV biology and pathogenesis. The productivity of DATRI, to date, has also been extremely limited, in terms of both published results and the availability of relevant clinical specimens to qualified investigators. It is thus difficult for the Panel to support the continuation of the DATRI program (from the perspective of the program's contribution to etiology and pathogenesis research). The Panel believes that resources currently devoted to this program would be better spent on more productive activities. The SPIRAT program is the newest of the clinical trial programs, and its productivity cannot be fairly assessed at present. Ideally, this program will support innovative studies directed at the most pressing research questions at the interface between the basic and clinical sciences. However, the Panel is concerned that certain constraints that are currently placed on the types of studies that can be supported by this mechanism do not foster this goal (such as the nature of the corporate collaboration and anticipated time frame with which a proposed therapy might actually enter clinical use). Further, the SPIRAT might, if well conducted, set the standard for translational research efforts. It is not clear that pursuing studies that are already well supported by other mechanisms or are likely to teach us little about the pathogenic mechanisms of HIV infection that might be relevant to designing better therapeutic approaches (such as HIV gene therapy) represent the best use of the SPIRAT mechanism. We encourage the DAIDS staff to apply the rigorous standards, outlined elsewhere in this report, for defining research priorities, encouraging productivity, and facilitating access to the oversight of the SPIRAT program.

NIAID supports an impressive intramural and extramural HIV/AIDS program. Overall, the HIV/AIDS-related collection of grants focuses on a number of highly relevant and related topics (e.g., immune cell function and OIs); however, the Institute has coded a large number of clinical trial-associated grants (U01s) as pathogenesis that have no real pathogenesis function. These grants need to be re-coded and funded from funds dedicated to clinical trials. There were also enormous expenditures (i.e., RMS expenditures) that could not be accounted for, based on

information available in the ARIS database. Such expenditures, loosely designated as management costs, and several small-equipment grants brought the "unaccountable or not analyzed" grant cost to a high level ($24 million). The Panel could not, therefore, assess whether or not these funds were appropriately spent on important AIDS research topics.

NCI

NCI has a long history of supporting productive research on retroviruses and was the birthplace for HIV research at the NIH. NCI investigators have made critically important contributions to the area of AIDS etiology and pathogenesis research. However, as is clear in recent evaluations of AIDS research at NCI (see the Bishop-Calabresi and Link Gay Men's Health Crisis [GMHC] reports), major problems have plagued the program. First, there has been an extraordinary imbalance between the levels of funds used to support intramural researchers versus extramural researchers. Second, as highlighted by others but also strikingly apparent in this Panel's analysis, it is difficult to consider large segments of the research supported by NCI's AIDS research dollars as truly AIDS-related research. Third, significant concerns have arisen regarding the quality and oversight of the NCI intramural AIDS research program. The Panel is aware of and applauds the efforts of the new NCI Director, Dr. Richard Klausner, to rectify these serious deficiencies. Thus, criticizing past deficiencies would at this stage be neither appropriate nor productive. We encourage Dr. Klausner to be exacting in his expectations for the quality and AIDS relevance of NCI's AIDS research effort and to strive to avoid unnecessary duplication with programs more appropriately conducted by other ICDs. His initial efforts to shift funds from the intramural program to the extramural program are encouraging, and these should be aggressively continued and expanded.

During this period of transition at NCI, it is appropriate to carefully consider what role NCI should play in future AIDS research efforts. In many ways, this time of transition should be a great opportunity to refocus and reinvigorate the NCI AIDS research program. There can be no doubt that it is NCI's responsibility to lead the effort on the study of AIDS-related malignancies. AIDS-related malignancies are a serious and increasing problem. Current treatments for AIDS-related malignancies, although somewhat more effective and less toxic than earlier approaches, are still grossly inadequate. Basic understanding of the pathogenesis of these malignancies should help in the derivation of new, more effective prevention and treatment strategies.

In addition to levels of morbidity and mortality that they cause in HIV-infected individuals, AIDS-related malignancies are important because they offer an opportunity to understand the underlying biology of these disorders. Many insights into the processes responsible for malignant transformation will likely emerge from the study of AIDS-related malignancies. The lessons learned from the study of these cancers will almost certainly prove relevant to understanding malignancies that occur in persons not infected with HIV. Further, perhaps no better circumstance than HIV infection is available to understand the role of immune surveillance in the control of malignancies, the contribution of aberrant immune system regulation to lymphomagenesis, and the role of viruses in human tumorigenesis. To not aggressively pursue these scientific opportunities and clinical challenges would be inexcusable.

The Panel encourages NCI to focus its attention and resources on the biology and pathogenesis of AIDS-associated malignancies and thereby accelerate the rate of discovery of better

therapeutic modalities. The Panel believes that the standards and approaches outlined elsewhere in this report can serve as useful guides for this effort.

NIMH

NIMH has played a leading role in coordinating efforts and focusing attention on neuro-AIDS in conjunction with the other lead Institutes, NINDS and NIAID. These efforts collectively have resulted in good clinical and pathological descriptions of this tragic and important complication of HIV infection, as well as progress in understanding how and when HIV enters the nervous system and hypotheses about how the virus causes neurological dysfunction. There is concern, however, over the dearth of substantive advances and publications in the field in the past few years, particularly in light of the level of investment of approximately $26 million a year. Remedies appear to be at hand. In analyzing the NIMH AIDS portfolio, more than half of the portfolio either could not be classified as even indirectly relevant to AIDS or was clearly unrelated to neuro-AIDS by even the most lenient criteria. The Panel commends efforts under way at NIMH to tighten the focus of the scientific portfolio, to redirect resources, and to continue to sponsor meetings to rekindle the kinds of innovative research that will move the field ahead again—as must be the case to develop effective treatment for neuro-AIDS in the future.

NINDS

NINDS has done a good job of classifying and funding its grants as HIV/AIDS-related. The most glaring problem with neuro-AIDS research at the NIH is that while tens of millions of dollars are spent annually on nervous system complications of HIV/AIDS by NIMH, NINDS, and NIDA, the progress in this field has been disappointing to date, as indicated by the publication numbers, representation at major HIV/AIDS or neuroscience conferences, and impact on favorably modifying the clinical course of HIV-associated neurologic diseases.

NCRR

NCRR supports two programs of critical relevance to AIDS etiology and pathogenesis research: the Regional Primate Research Center Program (RPRC) and the General Clinical Research Center Program (GCRC). The RPRC program is extensively discussed in the Animal Models section of this report.

The GCRC program has great potential to facilitate translational research activities concerning AIDS etiology and pathogenesis. Although a number of important studies in this area have been conducted in the GCRCs, the Panel believes that this resource has been underutilized to date. Further, the Panel is concerned about the level of review that goes into evaluating AIDS research activities at individual Centers. The current funding strategy, based essentially on a Center's past level of AIDS research funding, does not necessarily maximize the quality or AIDS focus of research conducted at the Centers nor reward GCRCs for being open to outside investigators or proactively advancing translational research activities in etiology and pathogenesis research. The Panel encourages NCRR to devise more effective evaluation and funding strategies to encourage the optimal use of this essential resource. Fostering improved

linkage between basic virologists, immunologists, and clinical researchers can and should be an important GCRC function.

NIGMS

As mentioned elsewhere in this report, the Panel believes that the effort of NIGMS to foster research on the structural biology of HIV and to encourage outstanding researchers to enter the field of AIDS research is a fine example to how the NIH can play a leadership role in AIDS research. We encourage other ICDs to study this model and to emulate it, as appropriate, in their own research planning and funding activities. We also encourage NIGMS to replicate this approach in other AIDS-related areas of research, such as the detailed evaluation of the HIV life cycle.

NIGMS has also done an admirable job of classifying grants as HIV/AIDS related.

NICHD

The study of pediatric HIV infections represents an important area of research, both from the perspective of identifying more effective prevention and treatment strategies, and as an opportunity to learn about the nature of the interaction of HIV with the immune system and the nervous system and its role in the metabolic and growth perturbations seen in infected individuals. Compared with its involvement in clinical trials research (through a collaborative relationship with NIAID to support the Pediatric ACTG [PACTG]), the level of investment of NICHD in etiology and pathogenesis research is small. The Institute funds few intramural efforts in this area. Its extramural efforts include involvement in the WITS and WIHS studies, and a modest number of R01 grants. In reviewing the NICHD program, the Panel was impressed by the commitment of the program staff to encouraging productive basic research on AIDS. However, the Panel believes that the Institute's efforts in this area have suffered by insufficient efforts to obtain expert external guidance in identifying research priorities and in designing innovative programs.

The PACTG is extraordinarily well situated to provide key insights into the pathogenesis of pediatric HIV infection, in both the areas of virus transmission and the progression and manifestations of HIV disease. Certain critical aspects of disease pathogenesis can be best studied in children, and interventional drug studies afford powerful tools to investigate many of these. Unfortunately, the Panel believes that the PACTG has not adequately capitalized on its unique opportunity to make progress in these areas. The major reason for this situation is the failure of the PACTG leadership to solicit external advice concerning the research agenda and the emerging opportunities for the program, or to establish productive collaborative interactions with outstanding basic investigators outside of the PACTG.

NIDDK

NIDDK appears to have funded and coded its AIDS pathogenesis program accurately. However, given that HIV/AIDS wasting and cachexia is the second most prevalent and serious AIDS complication, it is sad that this Institute supports only a relatively small research portfolio in the area of HIV/AIDS pathogenesis ($7 million). Better understanding of the interactions of HIV with the immune system and metabolic pathways in HIV-infected people is not only an essential need, but also a fascinating topic for future research.

NHLBI

The National Heart, Lung, and Blood Institute (NHLBI) has spent the majority of its pathogenesis money on the effects of HIV infection on target organs. In addition, the Institute has funded a variety of grants on OIs associated with the heart, lungs, and blood. The Institute has coded six grants associated with blood product quality as HIV pathogenesis that may not be, but this is nonetheless an HIV/AIDS-related subject. However, the relative priority placed on pursuing slight improvements in the safety of the blood supply from HIV infection at a time when it is already very safe might appropriately be reconsidered. NHLBI has funded a small amount of research ($3.7 million) on topics not directly germane to HIV/AIDS, mainly those related to hemoglobin research. Overall, the Institute is to be commended for funding and coding grants that appear to be mainly focused on HIV/AIDS-related issues.

NIDA

The NIDA AIDS research portfolio reviewed by the Panel displayed a number of problems concerning the relevance, accuracy of coding, and relative impact of the research conducted. Indeed the Panel's evaluation of NIDA's AIDS portfolio was limited by the fact that significant expenditures were so poorly described in the database that their relative merits could not be evaluated. The obvious association of injection drug use (IDU) and AIDS has generated a significant amount of research funding by NIDA. These research projects examine not only the sociobehavioral relationship between drug use and risk of HIV infection but also have been extended to study postulated biological relationships between drug use and disease pathogenesis. However, a significant number of the expenditures coded by NIDA as AIDS etiology and pathogenesis research did not focus on topics that the Panel views to be of high priority in this area. For example, the effects of opiates on the immune system (a major area of research support) cannot be viewed generically as an AIDS-related topic, and any new findings in this area would not be expected to alter the present state of AIDS clinical care. Further, as discussed in the body of this report, in the absence of more compelling evidence emerging from careful natural history studies that indicate that drug use directly contributes to the pathogenesis of HIV disease, the Panel does not believe that studies on the effects of drugs on immune system function should be supported with resources designated for AIDS etiology and pathogenesis research unless a clear scientific rationale can be presented to justify them. The Panel recommends redirection of NIDA's AIDS budget from studies that have little or no direct relevance to AIDS or that address low-priority topics to studies that are consistent with NIDA's important primary mission in AIDS research. It is important to note that the NIDA Director,

Dr. Alan Leshner, has made significant efforts recently to address these concerns and to increase the AIDS relevance and impact of the NIDA AIDS research portfolio.

NIAAA

NIAAA has spent a great deal (70 percent) of its HIV pathogenesis budget on topics not directly related to HIV/AIDS. Most of their funds are directed at studies of the effects of alcohol on general immune function not immune function as it relates to HIV infection. The Panel believes that these studies are not relevant to important AIDS research priorities. As previously discussed, unless carefully designed natural history studies provide evidence that alcohol use directly influences the course (rate or manifestations) of HIV disease, *in vitro* and tissue culture studies of the effects of alcohol on immunocompetent cells (or their constituent parts) should not be considered as ARR. If NIAAA feels that these studies of alcohol's effects on the immune system are important, these programs should be funded with non-AIDS resources. While this Institute spends little AIDS money in the pathogenesis area ($6 million), most of it should be redirected to areas where it will have greater impact.

NEI

All of the National Eye Institute (NEI) pathogenesis dollars reviewed were appropriately used for HIV/AIDS-related research. While cytomegalovirus (CMV) retinitis is a common, rather specific, and devastating AIDS OI, it is odd that so little of the HIV/AIDS budget is spent by NEI for research on this disease.

NIDR

Like the NHLBI, the NIDR appears to have spent and coded its small but focused AIDS pathogenesis dollars on topics surrounding HIV/AIDS as it pertains to oral tissues. Even its intramural programs are highly germane to the topic of HIV/AIDS. NIDR also funds several grants on *Candida*, which is of great concern in AIDS patients, and could possibly use additional funds (see the OI Subpanel report).

Appendix B

Biographies of Panel Members

Rafi Ahmed, Ph.D., is the Georgia Research Alliance Chair in Vaccine Research and Director of the Emory Vaccine Center. His research interests are in the areas of viral immunity and pathogenesis.

Mark Feinberg, M.D., Ph.D., currently serves as the Chair of the NIH Coordinating Committee on AIDS Etiology and Pathogenesis Research.

Dr. Feinberg has been engaged in basic research on the virology and pathogenesis of HIV disease since 1984. His current research activities focus on the study of host-virus relationships in pathogenic and nonpathogenic HIV and SIV infections, and on the application of emerging insights into the pathogenesis of HIV disease to the derivation of more effective therapeutic approaches for HIV-infected persons. Dr. Feinberg received his B.A. degree from the University of Pennsylvania and his M.D. and Ph.D. degrees from Stanford University. He served as an intern and resident in Internal Medicine at the Brigham and Women's Hospital, Harvard Medical School, Boston, and as a postdoctoral fellow in the laboratory of Dr. David Baltimore at the Whitehead Institute for Biomedical Research in Cambridge, MA. From 1991 to 1995, Dr. Feinberg was an Assistant Professor of Medicine and Microbiology and Immunology at the University of California, San Francisco, and Director of the UCSF Center for AIDS Research Virology Laboratory. During this period, he also served as an attending physician on the inpatient Medical and AIDS/Oncology Services and as a primary care physician in the outpatient AIDS Clinic (Ward 86) at San Francisco General Hospital. Dr. Feinberg joined the Office of AIDS Research in July 1995.

Dr. Feinberg has maintained an active interest in health and science policy issues related to AIDS. He has served on the staff of the National Academy of Science Committee on a National Strategy for AIDS in 1986, as a consultant for the Committee for the Oversight of AIDS Activities in 1988, and was a member of the Institute of Medicine/National Academy of Science panels on “HIV and the Blood Supply” and “Needle Exchange and Bleach Distribution Programs.”

Richard Gaynor, M.D., is currently Professor of Medicine and Microbiology at the University of Texas Southwestern Medical School. He is on external review boards for the NIH and the Veterans Administration and is on the editorial board of the *Journal of Virology*. Dr. Gaynor has extensive experience in studies of the regulation of gene expression of human retroviruses with a focus on HIV-1 and HTLV-I.

Gregg Gonsalves is Policy Director of the Treatment Action Group (TAG), the Nation's only community-based organization devoted solely to AIDS research advocacy. He is also on the Public Policy Committee of the Board of Directors of the AIDS Action Council in Washington, D.C. Mr. Gonsalves has worked on behalf of people with HIV since 1990, first as a member of ACT UP (AIDS Coalition to Unleash Power) Boston and then ACT UP/New York. He founded TAG in 1992 with a dozen other former members of the Treatment and Data Committee of

ACT UP/New York. Last year, he found out that he was himself HIV positive. He is the author of two reports on research on HIV infection: *AIDS Research at the NIH: A Critical Review* (1992, with Mark Harrington) and *Basic Research on HIV Infection: A Report from the Front* (1993), and has contributed to other reports by TAG and written for numerous other publications. Mr. Gonsalves was also the driving force behind the first research conference ever on long-term survivors of HIV infection, Immunologic and Host Genetic Resistance to HIV Infection and Disease, sponsored by the NIH in 1993. He has served as a consultant to the Antiviral Drugs Advisory Committee of the Food and Drug Administration. He recently participated in the first White House Conference on HIV and AIDS, where he reported to President Clinton on the state of research on vaccines and microbicide against HIV. His areas of special interest include AIDS drug development and regulation, clinical research methodology, and basic research on HIV infection.

Diane Edmund Griffin, M.D., Ph.D., is presently Professor and Chair of the Department of Molecular Microbiology and Immunology of the Johns Hopkins University School of Hygiene and Public Health and professor of Medicine and Neurology at the Johns Hopkins University School of Medicine. She received her M.D. (1968) and Ph.D. (1970) from Stanford University School of Medicine. Her current research interests are focused on understanding the pathogenesis of viral diseases. Infections of particular interest are those that cause arthropod-borne encephalitis, measles, and HIV-associated dementia. Her studies have identified the determinants of virus virulence, recovery from virus infection, and virus-induced immune suppression. She has served on the Virology study section at NIH, has chaired the Microbiology and Infectious Diseases Research Committee of the NIAID, and is a member of the World Health Organization Steering Committee for Respiratory Viruses and of the Research Advisory Board of the National Multiple Sclerosis Society. She is an Editor of the *Journal of Virology* and has published over 200 scientific articles.

Ashley T. Haase, M.D., is currently Professor and Head of the Department of Microbiology at the University of Minnesota. His long-standing interests are slow infections caused by viruses and virus-like agents, beginning 25 years ago with studies of infections of animals caused by lentiviruses, the subfamily of retroviruses to which HIV belongs. Dr. Haase has more recently turned his attention to HIV-1 infections, the role of covert infections in HIV-1 persistence, and the mechanisms and dynamics of immune depletion. Dr. Haase is the Chair of the AIDS Research Advisory Committee of the NIAID and has served on a number of review panels and task forces involved in the evaluation and strategic planning for research on AIDS and other infectious diseases.

Stephen C. Harrison, Ph.D., is Professor of Biochemistry and Molecular Biology at Harvard University, an Investigator in the Howard Hughes Medical Institute, and a Research Associate in Medicine at the Children's Hospital in Boston. He received his A.B. in Chemistry and Physics from Harvard College and his Ph.D. in Biophysics from Harvard University. He has developed the use of X-ray crystallography to yield images of virus particles in atomic detail and has used similar approaches to determine how transcriptional regulatory proteins recognize the specific DNA sequences to which they bind. His studies of HIV include crystallographic analyses of HIV reverse transcriptase and of CD4.

Richard Alan Koup, M.D., has been a Staff Investigator at the Aaron Diamond AIDS Research Center in New York City since 1991. He is also an Associate Professor of Medicine and Microbiology at the New York University School of Medicine and an Elizabeth Glaser Scientist of the Pediatric AIDS Foundation. He serves on several Government and private HIV research review committees. His research interests include immunity to HIV with emphasis on the role of cytotoxic T lymphocytes in AIDS pathogenesis, characterization of the humanized SCID mouse as a small animal model of HIV infection which can be exploited to define the role of cellular and humoral immunity in HIV disease, and vertical and horizontal transmission of HIV, with emphasis on mechanisms involved in resistance to transmission.

Norman L. Letvin, M.D., is Chief, Division of Viral Pathogenesis at Harvard Medical School's Beth Israel Hospital and Professor of Medicine, Harvard Medical School. He has extensive research experience using nonhuman primates as models for studying AIDS virus-specific T cell immunity and AIDS pathogenesis. He is a member of the editorial boards of numerous journals, including the *Journal of Immunology* and the *Journal of Virology*. He serves as a member of many NIH committees, including the NIAID AIDS Research Advisory Council and the Office of AIDS Research Advisory Council.

George Miller, M.D., is a world leader in elucidating the biology of Epstein-Barr virus (EBV), a human oncogenic virus. His contributions are basic to understanding latent viral infection, regulation of gene expression and viral oncogenicity. He has been at Yale University since 1969 and is presently the John F. Enders Professor of Pediatric Infectious Diseases, Professor of Epidemiology and Molecular Biophysics and Biochemistry. He is currently serving on the Burroughs Wellcome Fund Career Awards Advisory Committee, the Damon Runyon Scholar Award Committee, and Board of Scientific Advisors of St. Jude's Research Hospital. He is a member of numerous professional societies including the American Society for Clinical Investigation, the Association of American Physicians, the Infectious Diseases Society of America, the American Society for Microbiology (where he was past DNA Virus Chairman), and the American Society for Virology. Dr. Miller is recipient of several awards including the Squibb Award, Enders Award, Macy Faculty Scholar Award, and the American Cancer Society Scholar Award. He is presently on the Editorial Board of *Pediatric Research* and formerly served on the Editorial Boards of the *Journal of Virology*, *Virology*, and the *Journal of Infectious Diseases*, among others.

Bruce Rabin, M.D., Ph.D., Professor of Pathology and Psychiatry and Director of the Brain, Behavior, and Immunity Institute at the University of Pittsburgh School of Medicine. He is also Director of the Clinical Immunopathology Laboratory of the University of Pittsburgh Medical Center and is currently the President of the Psychoneuroimmunology Research Society. His research focuses on the mechanisms of stressor-induced immune alteration. His research has shown that psychological stress produces changes in immune system function which are associated with an increased susceptibility to viral infection and activation of latent viral infections. He is studying behaviors that can be used to prevent stress from altering immune system function, with a subsequent positive effect on health.

George M. Shaw, M.D., Ph.D., is presently Professor of the Departments of Medicine and Microbiology and Deputy Director of the Center for AIDS Research at the University of Alabama at Birmingham. He previously was the Associate Professor, Departments of Medicine

and Microbiology at the University of Alabama from 1988-1992. Dr. Shaw serves on several NIH Study Sections and is a member of the American Society for Clinical Investigators. He attended Dartmouth College in Hanover, New Hampshire, where he received a B.A. degree in Biology and then received an M.D. and a Ph.D. in Medicine/Immunology from Ohio State University in Columbus, OH.

Mario Stevenson, Ph.D., is a Professor in the Program in Molecular Medicine and Departments of Molecular Genetics and Microbiology at the University of Massachusetts Medical Center since October 1995. Previously, he was a professor in the Department of Pathology and Microbiology at the University of Nebraska Medical Center since 1988. Dr. Stevenson's research focuses on Molecular Biology of HIV and SIV and particularly functions of accessory gene products and determinants which influence virus infectivity for nondividing host cells. Dr. Stevenson serves on scientific advisory panels for the American Foundation for AIDS Research and NIH.

Bruce D. Walker, M.D., is Associate Professor of Medicine at Massachusetts General Hospital in Boston. He received his B.S. in Chemistry from the University of Colorado and his M.D. from Case Western Reserve University. Dr. Walker was Assistant Professor of Medicine for Harvard Medical School from 1989 to 1992. He has received many awards and honors, including the NIH Merit Award in 1994, and served on the American Society for Clinical Investigation in 1993.

Irving L. Weissman, M.D., is Professor of Pathology/Developmental Biology at Stanford University School of Medicine. He focuses his work on lymphocytes—cells in the blood stream that effect the body's immune system response. His laboratory developed an animal model, the SCID-hu mouse, in which the human immune system could be studied. Dr. Weissman received his B.S. from Montana State College and his M.D. from Stanford University School of Medicine. He completed postdoctoral studies at Oxford University in England and at Stanford. He joined the faculty of Stanford University School of Medicine in 1969. He was reelected to membership in the National Academy of Sciences in 1987, to the American Academy of Arts and Sciences in 1990, and received an Honorary Doctor of Science from Montana State University in 1992.

Steven Wolinsky, M.D., received his degree in 1979 from the University of Connecticut School of Medicine. His past research with Dr. Thomas Broker at the University of Alabama focused on the genetic characteristics of the replication kinetics and genomic organization of human papilloma virus (HPV). Currently, Dr. Wolinsky is principal investigator of a major NIH multisite contract at Northwestern University to investigate the correlates of protective immunity to HIV-1 infection to determine data for the eventual development of an efficacious HIV-1 vaccine.